THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME II MAY, 1926 NUMBER 3

VALVULAR DISEASES OF THE HEART
WITH SPECIAL REFERENCE TO THE PATHOGENESIS OF OLD VALVULAR DEFECTS *

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The primary object of this investigation is to trace the development of old valvular defects. This involves a detailed study of all forms of acute endocarditis, especially with reference to the manner of healing. We have available for study 280 cases of valvular heart disease, not including those of syphilitic origin.

We have classified the valvular diseases as follows:

I. Rheumatic endocarditis
   1. acute
   2. recurrent or chronic

II. Bacterial endocarditis
   1. acute { *a.* primary / *b.* secondary
   2. subacute

III. Old valvular defects
   1. inflammatory { Group 1 / Group 2
   2. calcified nodular — Group 3
   3. congenital

IV. Syphilis of the aortic valve

I. RHEUMATIC ENDOCARDITIS

1. ACUTE RHEUMATIC ENDOCARDITIS. A summary of eighteen cases of this condition is given in Table 1. The diagnosis is based upon the gross appearance of the lesions on the valves. Although there are no fundamental differences, it is convenient to distinguish

* Received for publication March 1, 1926

rheumatic and bacterial vegetations. The former are small, firm, discrete or fused to form a narrow ridge, and translucent to pale red in color. Their consistence is such that they do not become detached to form emboli. Bacterial vegetations are relatively large and vary in color from red to white. They are of soft consistence and portions readily break off to form emboli. The microscopic differences will be discussed later. Transition forms are occasionally seen, and frequently both types of vegetations are found in the same heart or even on the same leaflet. The cases classed as rheumatic are those in which no typical vegetations of bacterial type are found.

Seven of the eighteen patients were suffering with multiple acute arthritis at the time of death and were therefore typical clinical cases of acute rheumatic fever. Five others had clinical signs of systemic infection but had no arthritis. In the light of the postmortem findings these may also be considered acute rheumatic fever, since it is well known that rheumatic endocarditis may exist without arthritis. The case of chorea belongs definitely to the rheumatic group.

But there are five cases in which the endocarditis was an accidental postmortem finding. In Nos. 24–364 and 25–411 there are no clinical data. In the case of acute poliomyelitis, the rheumatic lesion may be interpreted as an independent terminal infection; but in the two cases of acute endometritis there is a strong suggestion that the endocarditis was produced by the organisms responsible for the uterine infection. Rheumatic endocarditis does occur secondary to infectious processes though much less frequently than the bacterial type.

Acute pericarditis was present in every case that died primarily of rheumatic fever, and this complication seems to be largely responsible for death in the acute stage.

Coincident with the formation of the vegetations there is a diffuse inflammation of the marginal part and often of the entire leaflet. The leaflet shown in Fig. 1 is opaque throughout; its capillaries are greatly dilated, and there are several small hemorrhages. Microscopically this leaflet shows an extensive lymphocytic exudate throughout. This diffuse distribution of the inflammation in the acute stage is important in the interpretation of the old valve defects to be discussed later on.

TABLE 1

Acute rheumatic endocarditis

Number	Age in years	Sex	Duration	Acute arthritis	Sepsis without arthritis	Acute pericarditis	Valves involved	Aschoff bodies	Cause of death	Glomerulonephritis
10–92	14	F	2 wks.	–	..	–	mitral	+	chorea	–
15–83	28	F	several months	+	..	+	mitral	–	rheumatic fever	?
16–272	23	M	1/12	–	+	+	mitral	+	rheumatic fever	–
16–326	18	M	?	–	..	–	mitral	–	acute poliomyelitis	?
17–106	4	F	3 wks.	+	..	+	mitral	–	rheumatic fever	–
20–319	3½	M	3 wks. +	+	..	+	mitral, aortic	–	rheumatic fever	?
22–185	6	F	2 mos.	+	..	+	mitral, tricuspid	+	rheumatic fever	?
22–209	28	F	3 days	–	..	–	aortic	–	acute endometritis	–
22–595	9	F	3 wks.	–	+	+	mitral, aortic, tricuspid	+	rheumatic fever	?
23–354	12	M	2 mos. +	–	+	+	mitral	+	rheumatic fever	?
24–1a	15	F	3 mos.	+	..	+	mitral, aortic	+	rheumatic fever	?
24–275	34	M	3 wks.	+	..	+	mitral	+	rheumatic fever	–
24–364	40	M	?	–	..	–	mitral	+	undetermined	–
25–163a	16	M	3 mos.	–	+	+	mitral, aortic	+	rheumatic fever	?
25–171	19	M	2 mos.	+	..	+	mitral, aortic, tricuspid	+	rheumatic fever	?
25–207	31	F	8 days	–	..	–	mitral	–	acute endometritis	–
25–319	3 mo.	M	3 days	–	+	–	mitral	–	rheumatic fever, meningocele	–
25–411	23	F	?	–	..	–	mitral	+	acute lysol poisoning	–

2. Recurrent or Chronic Rheumatic Endocarditis (Table 2). In this group all hearts are included that show acute lesions of rheumatic type along with thickened scarred leaflets. It is not possible to make an anatomic distinction between chronic and recurrent forms but this may sometimes be done clinically.

Clinical Features. In this group of eighteen patients, thirteen gave a definite history of one or more attacks of acute arthritis, and of these, two had arthritis at the time of death. The history was incomplete in four cases.

Sixteen patients were suffering from chronic cardiac disease, and of these, five died apparently of cardiac failure without any clinical signs of a terminal infection, two of lobar pneumonia, one from a bleeding gastric ulcer and one from an anesthetic. Of the remaining seven, five had clinical findings suggesting an active infection, but did not have arthritis, and two had typical rheumatic fever at the time of death.

The two patients that had no signs of chronic cardiac disease died suddenly, one from a gunshot wound, the other from an undetermined cause.

A case of this group may be recognized clinically when the symptoms and signs of an active rheumatic infection are present in association with the evidences of an old valvular defect. These conditions were fulfilled in only six cases, and even these were difficult to distinguish clinically from subacute bacterial endocarditis.

Gross Pathology. The vegetations are identical grossly with those of the acute rheumatic type described above. In nine hearts, only the previously thickened valves showed acute vegetations; but in three hearts the vegetations were found on the normal valves and not on the defective ones. In six hearts both kinds of valves showed vegetations, and in nine hearts, therefore, acute lesions were found on valves not previously diseased. In a recurrent infection there seems to be a definite tendency for more valves to become involved.

The appearance of the affected thin leaflets corresponds entirely to the acute rheumatic type; but on the thickened leaflets the vegetations are usually not prominent and are easily overlooked (Fig. 2). The situation of the vegetations is the same as in the acute type.

Considering both acute and chronic changes, the mitral valve was affected in 17 instances, the aortic in 14, the tricuspid in 6 and the pulmonary in 1. The mitral alone was involved in 3 cases, but no

other valve was affected singly. There is evidently a greater tendency for the original infection to attack the mitral value. (Table 2, mitral valve defect 17, aortic valve defect 8) (*cf.* also Table 1, mitral 19, aortic 7).

Structure of Rheumatic Lesions.[1] The stages preliminary to the appearance of the vegetations are not known with certainty since the disease is recognized only when they are present. In association with the smallest vegetations there is already a widespread inflammation throughout the marginal part of the leaflet. In 25–319 (Table 1) the clinical duration was only three days and the vegetations were few and very small. Portions of the leaflets between vegetations show many fibroblasts and polymorphonuclear leucocytes, as well as edema. In well developed cases, the margins of the leaflets apart from the vegetations may show a structure such as is shown in Fig. 3, *viz.*, many large fibroblasts, a few lymphocytes and polymorphonuclears, and an intact surface endothelium.

The smallest vegetations vary somewhat in structure, depending upon the relative proportion of fibroblasts, hyalin, and serous and cellular exudate. The most common type is shown in Fig. 4 (right-hand side). There is a dense collection of fibroblasts near the surface with a little hyalin at the surface. A few polymorphonuclears and lymphocytes are present. On the left-hand side of Fig. 4, the vegetation contains a large amount of hyalin. The endothelium is detached over the central part of the vegetations.

In some vegetations hyalin is a very prominent constituent (Fig. 6). It forms in masses within the leaflet and breaks through the endothelium.

A typical well formed vegetation is elevated from the surface and sometimes pedunculated (Fig. 7). The core is formed chiefly of fibroblasts, but there is a varying amount of serous exudate (edema) and cellular exudate (lymphocytes). Small capillaries are always present. There is a surface layer of hyalin under which the fibroblasts are somewhat more closely packed than elsewhere (Fig. 8). The surface endothelium is largely detached over the hyalin. In some places small platelet thrombi form on the rough surface (Fig. 5). Underneath the vegetation there is a marked inflammatory reaction, characterized by extensive perivascular lymphocytic infiltration and numerous small fibroblasts.

The vegetations seem to be merely localized swellings on the leaflet

TABLE 2

Recurrent rheumatic endocarditis

Number	Age in years	Sex	Duration of cardiac symptoms	Previous attacks of acute arthritis *	Arthritis at time of death	Sepsis at time of death	Valves previously involved	Valves with acute lesions	Weight of heart in grams	Aschoff bodies	Cause of death	Acute pericarditis	Old pericardial adhesions	Glomerulonephritis
13–74	16	F	8 mos.	5 yrs., 4 yrs., 3 yrs., 2 yrs., 8 mos.	–	–	mitral, I_2	aortic	enlarged	+	lobar pneumonia, C. F.	–	–	–
13–142	14	F	5 yrs.	5 yrs., 3 mos.	+	..	mitral, I. S.	mitral, aortic, tricuspid	400	+	C. F., rheumatic fever	–	+	–
15–377	47	M	2 yrs.	2½ yrs.	–	–	aortic, I_1 mitral, I_1	mitral	1061	–	C. F.	–	+	?
17–227	56	M	5 yrs.	many attacks	–	–	mitral, I_1 aortic, I_1	mitral	475	–	C. F., lobar pneumonia	–	–	–
18–123	35	M	3 wks.	?	–	–	aortic, I_2, mitral, S. I.	mitral	800	+	C. F.	–	–	–
18–204	21	M	0	?	–	–	mitral	mitral	350	–	gunshot, immediate death	–	–	–
20–153	37	F	6 mos.	6 mos.	+	..	mitral, I. S.	mitral, aortic tricuspid	410	+	rheumatic fever, C. F.	–	–	–
20–163	15	M	3 yrs.	–	–	+	mitral, S_2	tricuspid	250	–	C. F., acute tonsillitis	–	–	–
21–194	35	F	1 yr.	4 yrs.	–	+	mitral, S. I., aortic, I_1	mitral	440	–	C. F., sepsis	–	–	–

21–253	23	M	7 mos.	7 mos.	–	–	aortic, I_3, mitral, S. I.	mitral, tricuspid	575	+	C. F.	–	–	–
22–28	14	F	1 mo.+	2 yrs., several later	–	+	mitral, I. S.	mitral, aortic	400	+	acute pericarditis, C. F.	+	–	–
23–153	40	M	8 yrs.	8 yrs.	–	–	mitral, S_2, aortic, I. S., tricuspid, S_2, pulmonary, I. S.	mitral, aortic, tricuspid, pulmonary	600	–	C. F.	–	–	–
23–161	48	F	1 mo.	1 mo.	–	+	mitral, S. I.	mitral, aortic	550	+	C. F., acute pericarditis	+	–	?
23–480	35	M	?	2 mos.	–	–	aortic, I_3, mitral, I_1	aortic, mitral	800	+	C. F.	+	–	–
24–519	23	F	?	?	?	?	mitral, S. I.	mitral	325	–	?	–	–	–
24–2a	15	F	1 yr.	4 yrs.	–	+	mitral, I_2	mitral, aortic	300	+	C. F., rheumatic fever	+	–	?
25–112	36	M	several yrs.	?	–	–	aortic, I_3	tricuspid	800	+	C. F., gastric ulcer hemorrhage	–	–	?
25–621	41	M	10 yrs.	1 mo.	–	–	mitral, S_3	mitral	500	–	anesthetic, C. F.	–	–	?

Legend: C. F. = cardiac failure. S = stenosis. I = insufficiency. S. I. = chiefly stenosis. I. S. = chiefly insufficiency.
The degree of stenosis or insufficiency is indicated by the subnumbers 1, 2, 3.

* Months or years preceding death.

due to an uneven intensity of the inflammatory reaction. What appears grossly to be a single vegetation is usually found microscopically to be a series of small confluent vegetations (Fig. 5).

Different degrees of intensity of the inflammatory reaction are to be noted. In 25–163a the marginal part of the leaflet is involved throughout its cross-section and there is a hyaline layer on both surfaces (Fig. 9). The fibroblasts are large and numerous and some multinucleated forms are seen (Fig. 10). There are many mitotic figures.

The fibroblasts are the most conspicuous cells in a rheumatic lesion. They develop from the fixed connective tissue cells of the leaflet. They may appear as spindle-shaped, branched or rounded with abundant cytoplasm. The reaction is the same as in proliferative inflammation elsewhere. The cell body enlarges and becomes rounded. Cell division occurs repeatedly. Frequently multinucleated fibroblasts are seen. In one valve, 25–163a, a number of typical Aschoff nodules are found.[2] As far as one may judge from transition forms, the multinucleated cells, separate or in Aschoff nodules, are derived from fibroblasts.

Rheumatic inflammation is chiefly proliferative in character but it is not uncommon to find a few polymorphonuclears in the earlier lesions; and small lymphocytes are numerous, especially in the leaflet below the vegetation. The lymphocytes tend to collect around the capillaries. Areas of serous exudate (edema) are often seen in the vegetations and elsewhere, and this is one cause of the swelling.

Dense hyaline material is found constantly on the surface of fresh vegetations. Some small vegetations consist chiefly of hyalin (Figs. 4 to 6). It may also be found deep within the substance of the leaflet apart from vegetations (Fig. 11). It seems to be chiefly a coagulated exudate and not a product of tissue disintegration. When the hyalin breaks through the endothelium, platelets may accumulate upon it (Fig. 5). A platelet thrombus cannot be distinguished from this hyaline material except by its position. Fibroblasts may be found scattered through the hyalin but they are usually not so numerous as elsewhere.

The reaction in the leaflet apart from the vegetations is very important in determining the subsequent effects upon the valve. The marginal part of the leaflets, especially of the mitral and tricuspid

TABLE 3

Acute primary bacterial endocarditis

Number	Age, in years	Sex	Duration	Arthritis, time before death	Valves involved	Acute pericarditis	Aschoff bodies	Glomerulonephritis
11–128	42	M	2 days	?	mitral	–	–	–
14–209	21	F	1 wk.	?	mitral	–	–	mild acute exudative
14–232	55	F	5 wks.	–	mitral	–	–	–
15–159	54	M	10 days	?	mitral	+	–	–
15–391	43	M	3 wks.	?	aortic	–	–	–
16–54	35	M	2 wks.	–	mitral	–	–	–
16–128	19	F	5 days	?	mitral	–	–	–
17–31	19	M	3 wks.	–	aortic	–	–	glomerular abscess
19–197	34	F	6 days	?	mitral, aortic	–	–	–
20–2	18	M	5 wks.	?	aortic	–	–	–
21–124	78	M	4 wks.	1 mo., still present	mitral, aortic	–	–	–
22–148	19	F	4 wks.	1 mo.	aortic	–	–	embolic
17–213	43	F	2 wks.	2 wks., still present	all four	+	–	embolic

TABLE 4

Acute secondary bacterial endocarditis

Number	Age, in years	Sex	Duration	Arthritis, time before death	Valves involved	Acute pericarditis	Aschoff nodules	Primary disease	Glomerulonephritis
10–59	7	F	5 days	–	mitral	+	–	otitis media	–
12–18	33	F	10 days	–	mitral	–	?	acute endometritis	–
13–16	31	F	?	?	mitral	–	–	tuberculosis with cavities	(amyloid)
14–255	39	M	4 wks.	6 yrs.	aortic	–	–	lobar pneumonia	acute diffuse
16–89	30	M	2 wks.	4 yrs.	aortic, mitral	–	–	erysipelas	subacute diffuse
16–308	23	F	1 wk.	?	mitral	–	–	acute endometritis	–
16–358	62	M	?	?	mitral	–	–	postoperative peritonitis	–
16–381	23	F	a few days	?	mitral	–	–	acute endometritis	–
17–233	38	F	?	has chronic arthritis	mitral	+	–	abdominal tumor	–
17–248	38	F	a few days	?	mitral	–	–	acute endometritis	–
18–39	39	M	?	?	mitral	–	–	pernicious anemia	–
18–53	47	M	?	?	aortic	–	–	carcinoma of stomach	–
19–94	46	F	9 days	?	mitral	+	–	postoperative peritonitis	–
20–209	56	M	?	?	mitral, aortic	–	–	peritonitis (carcinoma of stomach)	–

20–267	25	F	?	?	mitral, tricuspid	–	–	acute endometritis	acute diffuse
20–388	38	F	?	many in past 2 yrs.	mitral	–	–	leukemia	–
20–428	65	M	1 wk.	?	mitral	–	–	influenzal pneumonia	–
21–150	21	F	4 wks.	?	mitral	–	–	acute endometritis	–
21–237	36	F	3 wks.	?	aortic	–	–	acute endometritis	–
21–307	54	M	10 days	2 mos.	mitral	–	–	primary hypertension	–
22–134	46	F	9 days	?	mitral	–	–	influenzal pneumonia	–
22–149	68	M	?	?	mitral	–	–	carcinoma of prostate	–
22–229	23	F	?	?	mitral	+	–	peritonitis	–
23–252	31	F	1 wk.	?	mitral, aortic	–	?	scarlet fever	?
24–212	26	M	?	–	mitral	+	–	multiple sclerosis	embolic
24–566	26	M	?	?	mitral, aortic, tricuspid	–	–	thrombosis of cavernous sinus	–
24–745	12	M	?	?	mitral	–	–	acute osteomyelitis	–
25–103	68	M	?	?	mitral	+	–	infected wound	–

valves, nearly always shows a diffuse inflammation. Rarely this is of an acute proliferative character (Figs. 9 and 10); but more frequently it is of a more chronic type with large numbers of small fibroblasts, prominent blood vessels and some lymphocytes (Fig. 12). The inflammation may extend through the distal half of the valve (Fig. 1) or even to its attached margin. A section through the center of the opaque part of the leaflet shown in Fig. 1 shows a lymphocytic infiltration with many small fibroblasts. It is easy to understand how this lesion may give rise to a thickened scarred valve in the course of healing.

The structure of the vegetations in the recurrent cases is identical with that of the acute rheumatic lesions except that in general the lesions on defective valves are less active. There are usually fewer lymphocytes, smaller fibroblasts and more collagenous fibers. Healing processes are more in evidence and healed or partially healed vegetations are found along with the active ones. The valve underlying the vegetation is composed largely of scar tissue (Fig. 13).

Healing of Rheumatic Lesions. Relatively few persons die during the acute stage of rheumatic endocarditis. Death is usually due either to deformities of the valves that occur in the course of healing or to the subsequent development of a bacterial endocarditis on the diseased leaflets. Evidences of healing were found in all the recurrent and in two of the acute cases (24–364 and 24–1a) of rheumatic endocarditis. In the vegetations the first change noted is the formation of many new collagenous fibers along with a decrease in the size of the fibroblasts. These cells soon recede to the size of fixed tissue cells, and in the denser parts of the scar they usually disappear entirely. The central part of the vegetation becomes a scar-like structure. The lymphocytes emigrate or disintegrate. The peripheral hyaline layer becomes more homogeneous and glassy (Figs. 14 and 15) and remains in this condition indefinitely. It is not absorbed and does not become organized. Hyalin in the deeper parts of the vegetation or in the body of the leaflet may likewise persist indefinitely or it may become calcified. Within the hyaline masses there are very few fibroblasts and these disintegrate without forming collagenous fibers (Fig. 15). The end result of healing of a rheumatic vegetation is scar tissue sometimes with a thin hyaline layer on its surface. In the body of the leaflet healing results in an

increased amount of fibrous tissue which commonly assumes the appearance of a scar. This topic will be discussed further in connection with old valvular defects.

II. Bacterial Endocarditis [3]

This group includes all cases of active endocarditis except the rheumatic and the syphilitic. The vegetations are larger and softer than the rheumatic type. Their consistence is such that portions may become detached to form emboli. Bacteria are commonly present in the vegetations and in the circulating blood, but they cannot be demonstrated in all cases. There are no fundamental distinctions from rheumatic endocarditis, and lesions of the rheumatic type are present in a large percentage of the hearts of this group; but all hearts in which some of the vegetations are large and soft have arbitrarily been classified as bacterial.

1. Acute Bacterial Endocarditis. On clinical grounds it is convenient to classify all cases of less than six weeks' duration as acute and those of longer continuance as subacute. The acute cases may be further subdivided into those in which endocarditis is the only prominent clinical finding (*primary*) and those in which endocarditis is definitely overshadowed by some major illness which causes death (*secondary*).

a. In the *primary* group (Table 3) there are thirteen cases. The clinical picture is that of severe septicemia with or without physical signs of endocarditis. One death was due to cerebral embolism. Associated infections, presumably secondary to the septicemia, were found in four cases, *viz.*, bronchopneumonia, meningitis and pericarditis.

The vegetations are usually large and soft, but some small firm lesions of rheumatic type were occasionally seen. Ulceration of the leaflets was present in only one instance. In ten of the thirteen hearts only one of the valves was involved.

Only four hearts were available for microscopic study of the valves. Two of these showed necrosis of the marginal part of the leaflet with large platelet thrombi, and an exudate of polymorphonuclears and lymphocytes within the valve. In both of these, areas of inflammation of rheumatic type were found on the inner surface of the leaflet midway between the free and attached margins.

TABLE 5

Subacute bacterial endocarditis

Number	Age, in years	Sex	Duration acute symptoms	Valves involved	Old valvular defect	Arthritis, time before death	Weight of heart, in grams	Aschoff bodies	Pericarditis	Duration chronic valvular disease	Rheumatic lesions	Glomerulonephritis
10–73	42	F	3 mos.	mitral	–	several attacks	393	–	–	..	–	?
10–76	25	M	3 mos.	mitral	–	?	normal	–	–	..	..	–
10–164	36	M	?	aortic	aortic, I_3	–	530	–	–	?	..	–
12–76	46	M	10 wks.	mitral	–	continuous during attack	310	–	–	..	..	–
12–131	33	M	3 mos.	mitral, aortic	mitral, S. I. aortic, S. I.	–	460	–	–	?	+	subacute diffuse
13–100	39	M	?	aortic	aortic, I_2	?	675	–	–	?	..	embolic and mild acute diffuse
13–165	33	M	4 mos.	mitral, aortic	aortic, I_3	a few years	640	–	–	0	+	acute diffuse
13–180	63	M	?	mitral	mitral, S_2	?	normal	–	acute	2 yrs.	–	mild acute diffuse
13–189	48	M	3 mos.	mitral	mitral, I_2	–	675	–	–	0	..	embolic
13–190	35	F	6 mos.	mitral	–	20 yrs., 13 yrs., many other attacks	525	–	old	..	+	acute diffuse
14–49	25	M	3 mos.	aortic, mitral	aortic, I_3, mitral, S. I.	several attacks	575	–	–	0	–	acute diffuse

14–207	43	M	6 mos.	aortic	aortic, I_3	one	620	–	–	o	+	–
15–30	55	M	3 mos.	aortic, mitral	aortic, I_2, mitral, S. I.	?	475	–	–	o	+	–
15–81	35	M	6 mos.	mitral	mitral	–	575	–	–	o	..	–
15–97	29	F	9 wks.	mitral	–	?	normal	–	–	..	+	acute diffuse
15–176	42	M	6 mos.	aortic, mitral	aortic, S_3, mitral, I_1	–	480	–	–	o	..	–
15–209	35	F	?	mitral, aortic	mitral, I. S., aortic, S. I.	?	425	–	–	?	..	mild acute diffuse
15–312	24	M	9 mos.	aortic, mitral	aortic, S. I., mitral, I_1	9 mos.	723	–	–	o	+	embolic
15–393	59	M	6 mos.+	mitral, aortic	–	?	normal	–	–	..	+	–
16–124	45	M	5 mos.	mitral	–	?	400	–	acute	..	+	embolic
16–152	6	F	3 mos.	mitral	–	–	243	–	acute and old	..	–	acute diffuse
16–203	61	M	2 mos.	aortic	aortic, S. I.	?	680	–	–	?	–	?
16–251	33	M	10 wks.+	mitral, tricuspid	mitral, S_3	21 mos.	574	–	–	15 mos.	..	embolic
16–295	11	F	2 mos.+	mitral, tricuspid	mitral, I_1	2 yrs. (chorea)	250	+	–	2 yrs.	+	embolic

TABLE 5 — *continued*

Number	Age, in years	Sex	Duration acute symptoms	Valves involved	Old valvular defect	Arthritis, time before death	Weight of heart, in grams	Aschoff bodies	Pericarditis	Duration chronic valvular disease	Rheumatic lesions	Glomerulonephritis
16–413	38	M	3 mos.	aortic, mitral	aortic, I. S., mitral, I_1	5 yrs.	860	–	–	?	+	embolic
17–28	29	M	11 mos.	aortic, mitral, tricuspid	aortic, I_2, mitral, I_2	11 yrs., 6 yrs.	690	+	acute	0	+	embolic
17–36	29	F	6 mos.	mitral	mitral, I_1	9 yrs., many since	250	–	–	14 yrs.	..	embolic, mild acute diffuse
17–174	28	M	7 mos.	mitral	mitral, I. S.	10 yrs.	565	+	–	4 yrs.	..	–
17–202	25	M	8 mos.	mitral	mitral, I_2	10 yrs., 9 yrs.	640	–	old	6 yrs.	..	acute diffuse
17–260	25	M	7 mos.	aortic, mitral	aortic, I_2 mitral, S_2	11 yrs., 7 mos.	570	–	–	11 yrs.	–	embolic, severe
18–102	23	M	4 mos.	aortic, mitral	aortic, I_2	?	690	–	–	0	+	–
18–105	13	F	11 mos.	mitral	–	–	350	–	–	..	–	–
18–122	30	M	3½ mos.	mitral, aortic	–	–	565	–	–	..	..	acute diffuse
18–175	34	M	8 mos.	aortic, mitral	–	?	480	–	–	..	..	embolic, severe
18–178	24	F	?	mitral, aortic	mitral, S_2	?	410	–	–	?	..	?
19–23	31	F	7 wks.	aortic	–	–	300	–	–	..	–	glomerular hemorrhages

19–141	55	M	6 wks.	aortic	–	–	325	–	–	..	+	–
19–161	23	F	8 mos.	mitral, tricuspid	–	–	365	–	acute	..	+	embolic, severe
19–264	29	M	?	mitral	–	2 yrs., 1 yr.	435	–	–	..	+	chronic diffuse
19–273	66	M	2 mos.	aortic	–	–	480	–	–	..	+	–
19–276	16	M	?	aortic, tricuspid	aortic, I_3	?	620	–	–	2 yrs.	–	acute diffuse
20–88	51	M	6 wks.	aortic, tricuspid	–	?	314	–	–	..	..	–
20–122	63	M	?	aortic	–	?	450	–	acute	..	–	–
20–165	43	M	6 mos.	aortic, mitral	–	–	625	–	–	..	+	–
20–296	16	M	7 wks.	mitral	–	–	330	+	–	..	..	–
20–326	28	M	2 mos.	mitral, aortic	mitral, I_1, aortic, I_2	12 yrs., 8 yrs., 5 yrs., 2 yrs.	920	–	old	several yrs.	+	?
20–344	12	F	5½ mos.	mitral, aortic	–	5½ mos.	280	–	–	..	+	embolic, severe
20–368	18	M	6½ mos.	mitral	–	?	340	–	acute	..	+	embolic and acute diffuse
21–45	55	M	4 mos.	mitral, aortic	–	–	420	+	–	..	+	embolic, severe
21–65	52	M	?	mitral	–	?	400	–	–	..	+	embolic
21–283	24	M	7 mos.	mitral	–	–	400	–	–	..	..	embolic
21–414	50	M	2 mos.+	mitral	–	35 yrs.	enlarged	–	old	..	–	–

TABLE 5 — *continued*

Number	Age, in years	Sex	Duration acute symptoms	Valves involved	Old valvular defect	Arthritis, time before death	Weight of heart, in grams	Aschoff bodies	Pericarditis	Duration chronic valvular disease	Rheumatic lesions	Glomerulonephritis
21–468	36	M	14 wks.	mitral	–	3½ mos.	450	–	–	..	..	?
21–513	42	M	10 wks.	aortic, mitral	–	8 yrs.	545	–	–	..	+	?
21–559	28	M	14 wks.	mitral, aortic	mitral, I_2	–	490	–	–	0	..	–
22–217	55	M	6 wks.	tricuspid	–	–	245	–	–	..	–	–
22–287	50	M	?	aortic, mitral	aortic, I. S., mitral, I_1	4 yrs., 8 mos.	660	–	–	4 yrs.	+	–
22–418	41	M	?	aortic	–	?	675	–	–	..	–	–
22–465	21	M	?	aortic	aortic, I_2	?	450	–	–	3 yrs.+	..	?
22–554	43	M	5 mos.	aortic, mitral	–	?	610	–	acute	..	+	chronic diffuse
23–390	45	M	?	aortic	–	–	575	–	–	..	+	acute diffuse
23–484	46	M	3½ mos.	aortic, mitral	aortic, S. I.	9 yrs.	725	–	acute	9 yrs.	+	–
23–508	76	M	7 wks.+	aortic, mitral	aortic, S. I.	several attacks past few yrs., 12 wks.	550	–	–	?	–	embolic
24–4	30	M	5 mos.	tricuspid	–	–	300	–	–	..	..	embolic
24–91	39	M	11 mos.	aortic	aortic, I. S.	20 yrs., 11 mos.	580	–	–	10 yrs.	+	embolic

24–121	59	M	7 mos.	aortic, mitral	–	–	560	–	old	..	+	–
24–241	23	F	11 wks.	aortic, mitral	–	7 yrs., 11 wks. to present	330	–	old	..	+	embolic
24–605	35	M	3½ mos.	aortic	–	–	550	–	–	..	+	embolic
24–769	14	F	5 mos.+	mitral	mitral, I_1	chorea, 3 yrs., 7 mos., 5 mos.	255	+	–	3 yrs.	+	embolic, severe
24–770	10	F	4 mos.	aortic	–	4 mos.	380	–	acute	..	+	?
24–807	20	F	6½ mos.	mitral, tricuspid	–	–	400	–	–	..	–	acute diffuse
25–142	4	F	6 wks.	mitral	–	has chorea	125	–	–	..	..	–
25–362	42	M	6 wks.	pulmonary	–	–	420	–	acute	..	..	–
25–589	30	F	3 mos.	mitral, aortic	mitral, I. S., aortic, I_2	8 attacks past 12 yrs., present now	350	–	old	?	+	acute diffuse
11–122	51	M	6 wks.	mitral, aortic	mitral, S_3	16 yrs., 1 yr., several between	575	–	–	16 yrs.	+	–

Legend: S = stenosis. I = insufficiency. S. I. = chiefly stenosis. I. S. = chiefly insufficiency. The degree of stenosis or insufficiency is indicated by the subnumbers 1, 2, 3.

In the two others there were large fresh soft thrombi with an extensive exudative reaction within the leaflet. The leucocytes were chiefly polymorphonuclears. There was some proliferation. Numerous bacteria were found in the thrombotic material of one of these.

b. Twenty-seven cases of *secondary acute bacterial endocarditis* (Table 4) were studied. The clinical symptoms were always those of the major illness. The endocarditis was not recognized clinically in any case, but perhaps it might have been diagnosed in some had more attention been given to the heart. The heart lesion was not considered by the pathologist as the main cause of death in any instance. In this group are seven cases of puerperal sepsis following induced abortion. The inclusion of this disease presumably explains the preponderance of females.

In twenty cases there was clinical evidence of septicemia which was attributable to the major illness, but in the remaining seven the usual signs of infection were absent.

The mitral valve was affected twenty-five times, the aortic five times and the tricuspid once. More than one valve was involved in only four cases. In only one heart was the acute lesion found on a previously thickened valve. The vegetations cannot be distinguished grossly from those of subacute bacterial endocarditis. In general, however, they are fewer in number. Ulceration of a leaflet was found only once.

Six hearts of this group were available for microscopic study of the valves. Four showed a large soft thrombus with necrosis of the leaflet and a purulent exudate within the valve. In one of these the single vegetation was 1 cm. in diameter. Bacteria were very prominent in another.

In the fifth and sixth cases there was very little exudate, the lesions being of proliferative type with prominent evidences of healing.

The lesions of acute bacterial endocarditis do not differ in any essential respects grossly or microscopically from those of the subacute bacterial type. Any distinction that is made must therefore be based chiefly on clinical data.

2. Subacute Bacterial Endocarditis. Seventy-four cases of this group have been studied (Table 5). The literature on this form of endocarditis has previously been reviewed by one of us.[4] These cases correspond clinically with subacute bacterial endocarditis as defined by Libman.[5]

The duration of symptoms in our series was as follows: 6 weeks to 3 months, 27; 3 to 4 months, 9; 4 to 5 months, 2; 5 to 6 months, 9; 6 to 7 months, 7; 7 to 8 months, 3; 8 to 9 months, 1; 10 to 11 months, 3; indefinite duration, 13. All the patients died within one year of the first appearance of symptoms.

Thirty-one of the seventy-four patients gave a history of one or more attacks of *acute arthritis*, and in eleven of these the fatal illness began with such an attack. A valvular lesion associated with acute arthritis may therefore be of the subacute bacterial type. The number of attacks varied from one to eight, and some occurred as long as twenty years before death. Twenty-four patients had never had arthritis, and in the nineteen others the history was indefinite on this point.

Relation to Previous Valvular Disease. Twenty-three patients gave a definite history of chronic valvular disease. In fifteen the duration was from one to sixteen years, and in eight the exact duration was unknown. Fifteen of these twenty-three patients gave a history of acute rheumatic fever which apparently caused the valvular defect.

In thirty-four instances the leaflets were grossly thickened and scarred, indicating a previous inflammation; but, since a considerable amount of scar tissue may form during the course of a subacute case, only extreme thickening can be considered positive anatomic evidence of a previous old valve defect. In forty cases there was no clinical evidence of old valve defect and the valves were not notably thickened. Apparently over half the subacute cases begin on previously normal valves. It is to be noted that when old defective valves are present in these hearts they always show an active inflammation. Apparently they are more susceptible to infection than normal leaflets.

In several instances the endocarditis appeared to develop secondarily to some other infectious process, *viz.*, otitis media (2 cases), lupus erythematosus (1), empyema (1), tonsillitis (1).

In the 74 hearts the mitral was diseased in 56, the aortic in 44, the tricuspid in 9 and the pulmonary in 1. A single valve was affected in 38 instances; mitral 22, aortic 13, tricuspid 2, pulmonary 1. The most frequent combination was mitral and aortic, 29 hearts.

Gross Appearance of Valves. The diagnostic feature is the large soft vegetation, but the appearance of the valves varies widely with the

number and size of the vegetations, and the extent of ulceration, thickening and calcification. Ulceration with loss of substance of the leaflet was present in thirty-two hearts. The term "ulcerative" endocarditis can properly be applied only to this number. The ulcers vary from a diameter of a few millimeters to complete destruction of a leaflet. They are more frequently found on the aortic valve. In three cases there was perforation of a leaflet, and in two there were ulcers penetrating to the right auricle from the aortic area.

Varying degrees of calcification of the valves were noted in twenty-five hearts. Calcium is deposited in the thrombotic material and in the old hyaline scar tissue. In the former position it is commonly present in moderate amounts, such as to give a gritty feel when cut; in the latter position, however, it is often of bony density. Calcium is readily deposited in the larger thrombi independently of the stage of healing. Frequently it is found in definitely active vegetations and even in association with bacteria.

In addition to the larger vegetations, small firm vegetations of the rheumatic type can be seen grossly in about three-fourths of the hearts, if a careful search is made for them. Sometimes one valve shows only rheumatic vegetations, but usually both types are found on the same leaflet.

Situation of the Lesions in Active Endocarditis. (*a*) *Aortic valve.* In acute rheumatic endocarditis the vegetations were always found on the ventricular surface of the leaflet in a line about one-third the distance from the free to the attached margin. This corresponds to the line of contact of the leaflets when the valve is closed. In recurrent rheumatic endocarditis the situation of the vegetations was the same except in one case in which they were found only on the free margin of one leaflet. In twenty-one cases of the subacute bacterial type, the vegetations occupied the same position as in the rheumatic form, but in twelve other cases they extended from this line around the free edge onto the aortic surface. In one case they were found only on the free margin of the leaflet.

(*b*) *Mitral valve.* In the acute rheumatic type the line of vegetations was always on the auricular surface, 1 to 2 mm. from the free margin, with one exception in which the vegetations were larger and extended over the free margin onto the chordae. In the recurrent type the vegetations occupied the same position as in the

acute type with two exceptions, in one of which they were on the free margin only and in the other on the ventricular surface only, near the free margin. In eighteen cases of the subacute bacterial type the vegetations extended from a line 1 to 2 mm. back of the free margin for varying distances upon the auricular surface. In thirteen other cases they extended from the auricular surface around the free margin onto the ventricular surface. In five hearts the vegetations were found only on the ventricular surface of the aortic leaflet of the mitral, extending from the central part of its surface toward the free margin. In all five of these the adjacent aortic leaflet also showed similar vegetations. A vegetation on this aortic leaflet may strike against the central part of the ventricular surface of the aortic leaflet of the mitral.

(*c*) *Tricuspid valve.* Acute lesions of both types were always found on the auricular surfaces of the leaflets near the free margin.

(*d*) In the single instance in which the *pulmonary valve* was involved, the lesion was of bacterial type and affected the margins as well as both surfaces of the leaflets.

Microscopic Structure. In forty-six hearts the valves were studied microscopically, one or two areas from each valve. Both exudative and proliferative forms of inflammation are usually found in the sections examined from each heart; but frequently one type of reaction predominates. Both types may be found in the same leaflet. The proliferative reaction is most common.

The exudative lesions are similar to acute exudative inflammation in other tissues. Rarely they are definitely purulent in character. The leucocytes are either polymorphonuclears or mononuclears. In one valve a number of embolic abscesses were found (Fig. 16). The thrombus overlying an exudative lesion is fresh and soft.

Proliferative inflammation is seen more frequently than the exudative. In the valve underneath the thrombus are large numbers of fibroblasts with relatively few leucocytes. The fibroblasts may be small and separated by a considerable number of collagenous fibers (Fig. 17); or they may be large with only a minimum of intercellular fibers (Fig. 18). In slowly progressive or healing lesions the fibroblasts tend to be smaller and the intercellular collagenous fibers more prominent. In sixteen hearts the proliferative lesions were prominent and the exudative inconspicuous. In five hearts large

multinucleated fibroblasts, such as occur in Aschoff bodies, were found (*cf.* Fig. 18). The histologic structure of the lesions in the valves seems to have no direct relation to the clinical course of the disease.

Necrosis of part of a leaflet is frequently seen. Ulceration is a direct result of necrosis.

In addition to the bacterial lesions just described, which predominate in these hearts, lesions of the rheumatic type were found in thirty-five of the forty-six that were examined microscopically. These vegetations have the same structure as those found in typical rheumatic endocarditis. In four hearts the tricuspid valve showed typical gross rheumatic vegetations but none of the bacterial type. Usually both types are found on the same valve. The rheumatic lesions may be continuous with the bacterial. The rheumatic vegetations were active in 22 hearts, healing in 9, and both active and healing in 4. In the 35 cases with rheumatic lesions 18 gave a positive history of rheumatic fever, 9 a negative history, and in 7 the history was incomplete. In the 31 cases with positive history of rheumatic fever, rheumatic lesions were present in 18 and absent in 5 (8 not examined). In 11 cases that began with acute arthritis, rheumatic lesions were present in 7 and absent in 2 (2 not examined). It cannot be said that the rheumatic vegetation is pathognomonic of rheumatic fever since it is found in three-fourths of subacute bacterial cases.

Evidences of healing are found in a great majority of these valves, and often the signs of active inflammation have largely disappeared. There may be active inflammation in one part of a leaflet and advanced healing in another part. In the leaflet itself the fibroblasts decrease in size while many new collagenous fibers are being formed. The leucocytes emigrate or disappear. The final result is dense scar tissue underlying a hyaline thrombus (Fig. 19).

The thrombus may soften and disintegrate, especially when it contains a large proportion of leucocytes. Portions may become detached to form emboli. Those portions that remain permanently attached to the leaflet soon become homogeneous in structure. They may persist indefinitely in this condition, or they may become calcified. Calcification may give rise to hard nodular masses or to diffuse hardening. Organization is rarely seen, and seems never of sufficient extent to convert a thrombus into scar tissue.

The most serious valvular defects result from necrosis and sloughing, but some deformities are due to the contraction of scar tissue. The importance of bacterial endocarditis in the production of old valvular defects will be discussed in a subsequent paragraph.

III. Old Valvular Defects [6]

This group includes cases of chronic valvular disease in which there were no clinical indications of active endocarditis, and in which the valves showed gross thickening and scarring. In 114 of the 130 cases of this group death was due to cardiac failure. In the 16 remaining cases the immediate cause of death was as follows: coronary sclerosis, 2; primary hypertension, 2; intestinal obstruction, 1; pyemia, 1; tuberculosis, 1; Addison's disease, 1; peritonitis, 1; suicide, 1; hemorrhage from gastric ulcer, 1; luetic aortitis, 1; cirrhosis of liver, 1; embolism of the stenosed mitral orifice, 1; and undetermined, 2.

The mitral valve was diseased in 95, the aortic in 82, the tricuspid in 13, the pulmonary in 3. The mitral alone was involved in 44, the aortic alone in 32, the tricuspid alone in none, the pulmonary alone in 3. The aortic and mitral were both diseased in 50 cases. The aortic, mitral and tricuspid valves were all three involved in 12 cases.

There were thirty-seven cases of pure mitral stenosis (*i.e.*, extreme stenosis with negligible insufficiency), and twelve cases with varying degrees of mitral insufficiency in which stenosis was negligible. In forty-three other hearts the mitral was both stenosed and insufficient, the stenosis dominating in thirty-five, the insufficiency in eight. In three hearts in which the mitral only was diseased, the lesion was not severe enough to cause any functional disturbance. In nineteen hearts an adherent pericardium was found, and in some of these it was the chief cause of the cardiac failure.

There were twenty cases of pure aortic stenosis, and seventeen with varying degrees of insufficiency without stenosis. In forty-one hearts the aortic valve was both stenosed and insufficient, the stenosis dominating in twenty-eight, the insufficiency in thirteen. In four hearts the lesion caused no functional disturbance. Aortic stenosis is not a rare type of chronic valvular disease.

The tricuspid lesions were usually of mild degree. The three pulmonary lesions were pure stenosis of congenital type.

Patients with mitral stenosis died at an earlier average age than those with aortic stenosis. In forty-three cases in which the mitral lesion was chiefly or entirely stenosis with a normal aortic valve, the average age at death was 41.7 years. In twenty-nine cases in which the aortic lesion was chiefly or entirely stenosis, with a normal mitral valve, the average age at death was 55.8 years.

The duration of symptoms of chronic valvular disease of all types was as follows: less than 1 day, 5 cases; 1 day to 3 months, 18; 3 to 6 months, 8; 6 to 12 months, 12; 1 to 2 years, 15; 2 to 3 years, 9; 3 to 4 years, 11; 4 to 5 years, 4; 5 to 10 years, 13; 10 to 20 years, 9; 20 to 34 years, 3; indefinite number of years, 4; and unknown duration, 14. With respect to the duration of symptoms there are no important differences between mitral and aortic stenosis.

There was a positive history of one or more attacks of rheumatic fever in fifty of the 130 patients, and a negative history in thirty. In fifty cases there was no mention of rheumatic fever. In one negative case the symptoms began after an attack of tonsillitis.

In sixteen cases of pure mitral stenosis without pericardial adhesions and without involvement of other valves, the average weight of the heart was 441 gm.; minimum weight 270 gm.; maximum 680 gm. The enlargement is chiefly right ventricular hypertrophy.

In thirteen cases of pure aortic stenosis without pericardial adhesions and without involvement of other valves, the average weight of the heart was 705 gm.; minimum 475 gm.; maximum 1130 gm.

The average weight of the heart in all the cases of chronic valvular disease was 580 gm.

Adherent pericardium (old adhesions) was found in nineteen cases, and acute pericarditis in six.

The most frequent gross change in the valves is thickening and stiffening with resulting loss of elasticity and narrowing of the orifice; but often there is retraction and curling with insufficiency which may be more pronounced than stenosis. The leaflets of the aortic valve are often fused together at the aortic attachment where they come into contact.

Calcification is a very common change in old defective valves, being present in varying degree in eighty-five of the 130 cases. The calcium is either distributed diffusely or in the form of large nodular

masses. Diffuse calcification was found in the mitral in forty-one instances and in the aortic in thirty. The calcium is deposited in the hyaline scar tissue within the leaflet.

Seventy-three of the 130 hearts of this group had been preserved and were available for careful gross and microscopic study. The remaining fifty-seven were described in the necropsy protocols, but no material except pieces of ventricular muscle was kept. Tables 6, 7 and 8 were made from the seventy-three preserved specimens. These hearts have been arranged in three groups for convenience of description: Group 1, in which the thickened valves are incompletely healed; Group 2, in which the valves are thickened and stiffened from newly formed fibrous tissue but show no unhealed areas; Group 3, in which the thickening of the leaflets is due chiefly to large calcareous nodules.

Group 1. Incompletely Healed Valves
30 Cases (Table 6)

The unhealed areas can usually be seen with the unaided eye, but often they are more readily recognized with a small hand lens. In eleven hearts they appeared as small firm pale vegetations, usually in the form of a slightly elevated ridge but sometimes very conspicuous (Fig. 20). Some of these valves are not distinguishable grossly from the recurrent rheumatic group, but usually the lesions are less prominent. In three hearts there were large ulcerated areas covered by a thin layer of thrombus (Fig. 22). In the remaining sixteen hearts the lesions appeared as small roughened denuded areas (Fig. 24).

Microscopic Structure. The thickened valves of this group are composed largely of dense fibrous tissue, often hyaline in structure, such as results from the healing of inflammatory processes in any tissue. But sections cut through the unhealed areas show a recognizable rheumatic or bacterial lesion in some stage of healing. It may be a well defined elevated vegetation, easily recognized as rheumatic. The one shown in Fig. 25 has a core composed of dense fibrous tissue in which capillaries are still present, and the surface hyaline layer is conspicuous. The one shown in Fig. 26 is of dense hyaline structure, but the surface hyaline layer may still be recognized on one side. A microscopic section of the vegetations seen in

TABLE 6

Old defective valves. Group 1. Incomplete healing

Number	Age, in years	Sex	Duration	Acute arthritis, time before death	Valves				Weight of heart in grams	Old pericardial adhesions	Calcareous nodules	Incomplete healing	Aschoff bodies
					mitral	aortic	tricuspid	pulmonary					
10–9	45	M	6 yrs.	20 yrs.	S. I.	S_2	I_1	–	540	–	–	mitral, raw area	–
10–142	47	M	?	?	S. I.	–	–	–	250	–	–	raw area	–
11–121	34	M	1 yr.	6 yrs., 3 yrs.	I_2	–	–	–	350	–	–	vegetations	–
12–117	54	M	16 mos.	?	I. S.	–	–	–	400	–	–	thrombus on large ulcer	–
12–168	27	M	4 yrs.	12 yrs., 8 yrs., 2 yrs.	S_2	S. I.	–	–	400	+	–	mitral, raw area	–
14–20	20	M	2 yrs.	?	S_2	I_1	o	–	370	–	–	tricuspid, vegetations; aortic, raw area	–
15–323	49	M	?	several attacks	S_2	–	–	–	325	–	–	thrombus on large ulcer	–
15–324	53	M	3 yrs.	28 yrs.	S. I.	I. S.	–	–	795	–	–	mitral, aortic, vegetations	–
16–16	29	M	27 mos.	10 yrs.	S_2	–	–	–	350	–	–	raw area	–
16–185	46	M	?	?	S. I.	–	–	–	320	–	–	thrombus on large ulcer	–
19–26	45	M	3 yrs.	?	S_2	–	–	–	510	–	–	raw area	?
19–286	51	M	1 yr.	?	S_2	–	–	–	550	–	–	raw area	–
20–157	61	M	3½ yrs.	?	S_2	S. I.	S_1	–	550	–	–	mitral, raw area	+
20–250	65	M	4 yrs.	?	o	S_2	–	–	715	–	aortic, mitral	aortic, raw area	–

20–358	21	F	12 hrs.	?	S_3	0	–	–	270	–	–	aortic, vegetations	–
20–433	57	M	5 mos.	40 yrs.	0	S_3	–	–	720	–	aortic, mitral	raw area, one leaflet	–
20–463	37	M	3 yrs.	19 yrs., 13 yrs., 4 yrs., 3 yrs.	I. S.	I. S.	–	–	825	–	aortic	mitral, aortic, raw area	–
21–259	52	F	2 wks.	–	S. I.	–	0	–	325	–	–	tricuspid, vegetations	–
21–285	53	M	10 yrs.	20 yrs.	–	I_3	–	–	475	–	aortic	raw area	–
21–416	46	M	6 wks.	20 yrs.	I. S.	I. S.	–	–	900	+	–	mitral, vegetations	–
21–473	58	F	7 mos.	?	S. I.	–	–	–	550	–	–	raw area	–
21–485	60	F	?	?	S_3	–	–	–	410	–	–	raw area	–
22–197	41	F	9 mos.	?	S_3	–	–	–	350	–	–	vegetations	–
23–142	35	M	5 yrs.	5 yrs.	–	S_3	–	–	850	–	–	raw area	–
23–324	42	M	3½ mos.	–	I. S.	S. I.	–	–	550	–	–	raw area	+
24–307	43	F	?	?	0	–	–	–	430	–	–	vegetations	–
24–482	40	M	?	?	S. I.	–	–	–	365	–	–	vegetations	–
24–613	38	F	?	?	0	–	–	–	375	–	–	vegetations	–
25–322	33	M	5 yrs.	?	S. I.	I.S.	–	–	690	–	–	aortic, mitral, raw areas	–
25–328	70	M	?	?	0	–	–	–	300	–	–	vegetations	–

Legend: S = stenosis. I = insufficiency. S. I. = chiefly stenosis. I. S. = chiefly insufficiency. The degree of stenosis or insufficiency is indicated by the subnumbers 1, 2, 3.

Fig. 20 is shown in Fig. 21. It consists of a rather thick layer of old hyaline thrombus resting on dense scar tissue. It suggests a healed bacterial type of lesion because of the thickness of the thrombus.

The raw areas show a variety of microscopic appearances. Occasionally fibroblasts are to be seen and there are other signs of low grade activity. Usually there are no signs of active inflammation. A layer of hyaline thrombus rests upon dense fibrous tissue (Fig. 27) or upon hyaline scar tissue (Fig. 28).

In one instance (25–322) the leaflet underlying the raw area showed areas of necrosis and numerous polymorphonuclear leucocytes as well as dense fibrous tissue. The ulcer shown in Fig. 22 likewise shows an active exudative inflammation within the substance of the valve (Fig. 23). Neither of these patients had any clinical signs of active endocarditis. They died apparently from the valvular defect and not from toxemia. The two hearts shown in Figs. 20, 21, 22 and 23 as well as one other are interpreted by us as old valvular defects resulting from subacute bacterial endocarditis. The other hearts of this group are considered to have developed from the rheumatic type of endocarditis.

There was a history of rheumatic fever in eleven of this group of thirty patients. The mitral valve was involved alone in 18; the aortic alone in 4; mitral and aortic, 6; mitral, aortic and tricuspid, 3. In four hearts there were calcareous aortic nodules characteristic of Group 3. In seventeen hearts one or more valves were partly calcified.

Group 2. Thickened Valves Composed of Dense Fibrous Tissue; No Unhealed Areas

28 Cases (Table 7)

In this group the valves have the same gross appearance and microscopic structure as those of Group 1 except that there are no areas of incomplete healing. All signs of active inflammation are absent except occasionally a little perivascular lymphocytic infiltration in the central part of the leaflets. The leaflets are composed of dense fibrous tissue which is often hyaline in appearance. At the surface one frequently sees a thin hyaline layer that suggests the surface hyaline layer of a rheumatic vegetation (Fig. 29). The valves of this group usually show areas that correspond in structure

to the undoubted healed rheumatic lesions found in recurrent rheumatic endocarditis (Fig. 15). The histologic structure, therefore, offers strong support for the interpretation of these valves as healed rheumatic endocarditis. The clinical and gross pathologic features parallel the cases of Group 1 in which this interpretation seems amply justified.

There was a history of acute arthritis in thirteen of the twenty-nine cases of this group. The mitral valve was involved alone in 12; the aortic alone in 2; mitral and aortic in 10; mitral, aortic and tricuspid in 5. The calcareous aortic nodules characteristic of Group 3 were found in two hearts.

Group 3. Cases of Aortic Stenosis Due to Calcareous Nodules; No Satisfactory Evidence of Inflammatory Origin

15 Hearts (Table 8)

In the fifteen hearts of this group, ten were pure stenosis and in the other five stenosis predominated but there was some insufficiency. There is a very marked thickening and stiffening of the leaflets due to large calcareous nodules within them (Fig. 30). The portions of the leaflets between the nodules are of normal thickness. There is usually fusion of the adjacent edges of the leaflets where they are attached to the aorta. The nodules are found on the aortic surfaces of the leaflets but when very large they cause projections on the ventricular surfaces also. The most frequent site is near the aortic attachment but they usually extend well out into the leaflet, frequently to its free margin. In one instance a row of nodules extended about 2 cm. up the root of the aorta. In twelve of the fifteen hearts there were similar nodules in the central part of the ventricular surface of the aortic leaflet of the mitral and frequently there was a continuous row of nodules from the aortic leaflet to those on the mitral.

The root of the aorta is almost invariably free of arteriosclerotic lesions. The nodules are of whitish color, never yellowish. There seems to be no relation between these nodules and the atheromatous lesions so frequently seen on the valves.

The surface endothelium is usually intact over the nodules but occasionally it is denuded so that the calcareous material is ex-

TABLE 7

Old defective valves. Group 2. Complete healing

Number	Age, in years	Sex	Duration	Acute arthritis, time before death	Valves				Weight of heart, in grams	Old pericardial adhesions	Calcareous nodules	Aschoff bodies
					mitral	aortic	tricuspid	pulmonary				
16–212	27	M	14 yrs.	14 yrs., several attacks since	S_3	I. S.	–	–	700	+	–	+
17–139	33	F	15 yrs.	–	S. I.	–	–	–	525	–	–	–
18–67	22	M	7 mos.	10 yrs., 5 yrs.	S_3	S. I.	–	–	750	–	–	–
18–124	32	F	18 mos.	12 yrs., 9 yrs.	I_3	–	–	–	675	+	–	?
19–58	39	M	4 yrs.	–	S. I.	I_1	–	–	585	–	–	–
19–120	43	F	6 mos.	29 yrs., 16 yrs., 3 yrs.	S_3	S. I.	S. I.	–	600	–	–	–
19–145	16	F	7 yrs.	–	S. I.	S. I.	S. I.	–	400	–	–	–
20–452	32	M	3 yrs.	5 yrs., 4 yrs.	S_3	I. S.	I_1	–	500	+	–	–
20–459	40	F	8 yrs.	–	S. I.	I_1	I_1	–	410	–	–	–
21–205	22	F	?	?	o	I_2	–	–	490	–	–	+
21–478	38	M	2 mos.	3 yrs.	S. I.	S. I.	–	–	400	–	–	–
22–147	47	M	several years	?	S_3	S.I.	–	–	600	–	aortic, mitral	–
22–300	28	M	6 yrs.	?	S. I.	–	–	–	550	–	–	–
22–309	39	M	6 yrs.	–	S_3	–	–	–	510	–	–	–

22–354	68	M	2½ yrs.	–	I_3	0	–	–	645	+	–	–
22–365	51	M	10 yrs.	many attacks 25 yrs. to 3 yrs.	S_3	S_3	–	–	640	–	–	–
22–476	48	M	many years	?	S_2	–	–	–	550	–	–	–
22–480	27	M	5 yrs.	8 yrs, 5 yrs.	S_3	I_1	S. I.	–	550	–	–	–
23–101	43	M	3½ mos.	5 yrs.	I. S.	S. I.	–	–	550	+	–	+
23–135	48	F	5 mos.	date (?)	S_3	–	–	–	350	–	–	–
23–142	35	M	5 yrs.	5 yrs.	–	S_2	–	–	850	–	–	–
23–741	22	M	10 yrs.	–	–	I_3	–	–	1150	+	aortic	–
24–14	42	M	4 yrs.	22 yrs.	I. S.	I.S.	–	–	610	+	–	–
24–29	44	F	3 yrs.	28 yrs., 10 yrs.	S_3	–	–	–	500	–	–	–
25–389	45	F	2 yrs.	?	S_3	–	–	–	360	–	–	–
25–574	39	M	3 mos.	–	S. I.	–	–	–	600	–	–	–
25–655	21	F	2 yrs.	7 yrs., 6 yrs., 2 yrs.	I. S.	–	–	–	420	–	–	–
25–666	64	F	4 yrs.	?	I_1	I. S.	–	–	595	–	–	–

Legend: S = stenosis. I = insufficiency. S. I. = chiefly stenosis. I. S. = chiefly insufficiency. The degree of stenosis or insufficiency is indicated by the subnumbers 1, 2, 3.

posed. The position of the nodules in no way corresponds to the vegetations of active endocarditis. Mönckeberg[7] finds that they originate within the fibrous layer of the leaflets which is continuous with the wall of the aorta.

Microscopic Structure. The nodules consist chiefly of masses of calcium. When decalcified a homogeneous material remains. It has not been determined what kind of tissue calcifies. Surrounding the calcium there is usually some loose connective tissue, containing fat both within the cells and in the stroma, such as is found in atheromatous areas in the aorta. There are also areas of hyaline fibrous tissue. Often the adjacent tissue is very vascular and contains many mononuclear leucocytes, a reaction which may be interpreted as a change preliminary to the replacement of the calcium by bone. In one valve true cartilage and bone were found. A similar reaction is often seen in the calcified mitral leaflets of an ordinary mitral stenosis in which no calcified nodules are present.

Our material is not sufficient to enable us to trace the development of these aortic nodules. They were found in the aortic valves in twelve out of 100 adults dead of primary hypertension. Their incidence in other diseases has not been studied by us. Mönckeberg[7] believes that they begin as small calcified areas in the fibrous layer of the valve leaflet near the aortic attachment and gradually increase in size and number until an aortic stenosis may develop. He considers them entirely unrelated to inflammations of the valves.

These calcareous aortic nodules were found in four hearts of Group 1 and two hearts of Group 2 (see Tables 7 and 8), in fifteen out of fifty-four cases of subacute bacterial endocarditis and in three cases of recurrent rheumatic endocarditis. Whether they are the result of the inflammation in these valves or merely accidentally associated with it was not determined. It is to be noted that they were present in one person only 22 years old (23–741, Table 7).

Small calcified nodules are sometimes found in thickened leaflets at the site where vegetations occur. These seem not to be related to the aortic nodules just described, although they cannot be distinguished microscopically.

Calcareous nodules similar to those on the aortic valves are found occasionally on the ventricular surface of the marginal leaflet of the mitral at its attachment to the ventricle. These may occur independently of any other lesion in any valve.

TABLE 8

Old defective valves. Group 3. Calcified nodular type

Number	Sex	Age, in years	Duration	Acute arthritis, time before death	Valves				Weight of heart, in grams	Old pericardial adhesions	Calcareous nodules	Aschoff bodies
					mitral	aortic	tricuspid	pulmonary				
15–38	M	66	9 wks.	1 yr.	o	S. I.	–	–	600	–	aortic, mitral	–
18–38	F	70	1 hr.	?	o	S. I.	–	–	425	–	aortic, mitral	–
18–143	M	51	10 yrs.	21 yrs.	–	S_3	–	–	600	–	aortic	–
18–167	M	50	1 yr.+	?	o	S_3	–	–	780	–	aortic, mitral	–
19–93	M	40	2 mos.	–	o	S_3	–	–	760	–	aortic, mitral	+
19–213	M	68	3 wks.	–	–	S_3	–	–	650	–	aortic	–
21–49	M	59	2 yrs.	?	o	S. I.	–	–	795	–	aortic, mitral	–
21–433	M	71	1 yr.	–	o	S_3	–	–	475	–	aortic, mitral	–
22–99	M	50	?	?	o	S_3	–	–	560	–	aortic, mitral	–
23–112	M	56	7 yrs.	?	o	S. I.	–	–	575	–	aortic, mitral	+
23–236	M	70	20 yrs.	?	o	S_3	–	–	500	–	aortic, mitral	–
23–320	M	44	?	?	o	S_3	–	–	1130	–	aortic, mitral	+
25–82	M	64	2 yrs.	?	–	S. I.	–	–	725	+	aortic	–
25–104	M	38	2 yrs.+	–	o	S_3	–	–	575	–	aortic, mitral	–
25–586	M	66	1 yr.+	?	o	S_3	–	–	500	+	aortic, mitral	–

Legend: S = stenosis. I = insufficiency. S. I. = chiefly stenosis. I.S. = chiefly insufficiency. The degree of stenosis or insufficiency is indicated by the subnumbers 1, 2, 3.

The average age of the twenty-one cases with aortic nodules is 54.5 years. Excluding the three youngest cases the average is 58 years. Apparently this type of valvular disease usually does not produce symptoms until late in life.

Nineteen of the seventy-three hearts with old valvular defects that are listed in Tables 6, 7 and 8 were examples of aortic stenosis (chiefly or entirely stenosis) without involvement of any other valve, and it is to be noted that in seventeen of these the aortic defect was due to calcareous nodules. Aortic stenosis in the absence of involvement of any other valve is therefore usually due to calcareous nodules.

Discussion

The initial stages of acute endocarditis are not definitely known. It has not been recognized in the absence of vegetations. There is a diffuse inflammation throughout the part of the leaflet adjacent to the free margin in the earliest stages, but it is not known whether this precedes the vegetations or *vice versa*. The study of serial sections from early cases, however, gives one a strong impression that the inflammation begins within the leaflet and extends to the surface, resulting in a vegetation. When only a few vegetations are present they are almost invariably situated on the inner surface along the line where the leaflets come into contact, but when there are many they often cover both surfaces of the leaflet, especially near its free margin. It may be inferred, therefore, that the trauma of contact has some causal relation to the first vegetations but not to those that form subsequently. It is now known that normal valves are supplied with blood vessels (Bayne-Jones,[8] L. Gross,[9] Kerr [10]) and that it is therefore anatomically possible for bacterial emboli to lodge within the valves as was maintained by Köster,[11] Rosenow [12] and others. We have no new observations as to the route of the primary infection except the finding of numerous bacterial emboli in one valve (Fig. 16).

In five hearts with aortic bacterial lesions the only mitral vegetations were situated on the central part of the outer surface of the aortic leaflet. In these instances the mitral lesion probably resulted from contact with an infected aortic leaflet.

To understand the structure of old defective valves it is very im-

portant to note that in the acute stages the vegetation is not the only lesion but that there is a diffuse inflammation of the leaflet, always in its distal part and often extending well toward its attached margin (Figs. 1 and 12). This is the reason why an old defective valve leaflet is commonly thickened throughout, with the maximum involvement near the free margin.

Rheumatic vegetations are largely proliferative in character. There are some lymphocytes and occasionally a few polymorphonuclears, but most of the cells are fibroblasts. There is practically no necrosis or ulceration and there is no organization since there is almost no material to be replaced. Lymphocytes are numerous in the valve apart from the vegetations. Healing occurs readily and always results in thickening of the leaflet, since the fibroblasts form many new collagenous fibers. As in any healing inflammation the newly formed fibrous tissue contracts, compressing the blood vessels and forming scar tissue. In time the scar tissue becomes hyaline in structure and it frequently becomes calcified. The thin layer of hyaline material on the surface of fresh rheumatic vegetations can often be recognized in old defective valves long after all signs of active inflammation have disappeared (Fig. 29).

In recurrent rheumatic endocarditis there is either an activation of a latent infection or a reinfection. Fresh vegetations form on valves already thickened by a previous inflammation and fresh leaflets become involved. Each attack leaves the valves thicker and more rigid than they were previously.

It is only a short step from the recurrent rheumatic to the old defective valve. The inflammation subsides and the clinical picture changes from infection to valvular defect. There is often a striking gross resemblance between these two stages (Fig. 20), though they may be distinguished by the clinical history and microscopic structure. Partially or completely healed vegetations may be found (Figs. 25 and 26), and in the raw areas the remnants of rheumatic inflammation are readily recognized (Fig. 28). Twenty-seven of the old defective valves of Group 1 show incompletely healed lesions recognizable as rheumatic. When the valves are completely healed (Group 2) the evidence of a rheumatic origin is not so obvious; but they are strikingly similar in structure to known healed rheumatic lesions (*e.g.*, those of recurrent rheumatic endocarditis, *cf.* Fig. 15 with Fig. 29), and they are parallel in clinical and gross pathologic

features to Group 1. Fifty-five of the seventy-three old defective valves are interpreted as of rheumatic origin.

Bacterial lesions differ from rheumatic only in the intensity of the inflammatory reaction. There are no sharp distinctions. Exudation is more abundant, the fibroblasts are more numerous, thrombi form on the injured areas and there is often necrosis and ulceration. Healing processes are found almost constantly but complete healing rarely occurs. The leaflet becomes fibrous and hyaline in certain parts. The thrombus soon becomes homogeneous. Portions may become detached. It may persist indefinitely as a hyaline thrombus or it may become calcified. We have found no evidence that organization occurs to any appreciable extent. Only three of the seventy-three old defective valves are interpreted by us as healed bacterial lesions, but even these were not clinical examples of bacterial endocarditis.

Rheumatic vegetations were found in three-fourths of the hearts of subacute bacterial endocarditis, and numerous transitions between the two types of vegetations were seen. Unless the improbable assumption is made that three-fourths of the subacute bacterial cases have a simultaneous acute rheumatic infection, it must be granted that rheumatic and subacute bacterial endocarditis are caused by the same organism.

Glomerulonephritis was found in 38 of 64 cases of subacute bacterial endocarditis. The type of glomerulonephritis was embolic in 19, acute diffuse in 13, subacute or chronic diffuse in 3, and a combination of embolic and acute diffuse in 3. Diffuse glomerulonephritis as a complication of subacute bacterial endocarditis is about as frequent as the embolic form. Baehr and Lande [13] called attention to this relationship in 1920.

Aschoff bodies were found in the different forms of endocarditis as follows: acute rheumatic, 61 per cent; recurrent rheumatic, 55 per cent; acute bacterial, 0 per cent; subacute bacterial, 8 per cent; old valvular defects, 10 per cent.

The calcified nodular type of old valvular defect may originate entirely independently of an inflammatory process, as Mönckeberg believes; but its frequent association with known inflammatory lesions has not been satisfactorily explained. It is noteworthy also that Aschoff bodies were found in the myocardium in three cases of this group.

Summary

In addition to the vegetations in acute endocarditis there is a diffuse inflammation always in the free edge and often involving the greater part of the leaflet. This circumstance explains the uniform thickening so commonly seen in old defective valves.

Rheumatic vegetations are composed chiefly of fibroblasts, and in the process of healing they readily become converted into fibrous tissue. There is no ulceration and no organization. Fifty-five of seventy-three old defective valves are considered the result of rheumatic endocarditis, and in twenty-seven of these incompletely healed rheumatic lesions were recognizable.

Bacterial endocarditis is a more intense inflammation than the rheumatic. Proliferation predominates but exudation is often prominent. Large thrombi are formed on the raw surfaces and there is often ulceration. Healing consists in the conversion of the leaflet into scar tissue. Such portions of the thrombi as do not become detached persist indefinitely without becoming organized, although they may become calcified. Complete healing rarely occurs. Three of seventy-three old defective valves were interpreted as the result of bacterial endocarditis.

Transitions between rheumatic and bacterial vegetations are frequently seen. Rheumatic vegetations were found in association with bacterial in three-fourths of the cases of subacute bacterial endocarditis.

Fifteen of seventy-three old defective valves belong to the aortic calcified nodular group. The etiology of this type is unknown. There is no satisfactory evidence that it is of inflammatory origin, and it seems unrelated to atheroma. Aortic stenosis in the absence of disease of any other valve is usually of this form.

Stenosis is more frequent than insufficiency in old defective valves.

The only old pulmonary valve defects seen were of the congenital type (three cases of pulmonary stenosis).

An acute rheumatic endocarditis may terminate in several different ways: (*a*) death during the acute stage from toxemia; (*b*) partial or complete healing followed after a variable interval by the reappearance of fresh rheumatic vegetations (recurrent rheumatic endocarditis); (*c*) partial or complete healing followed by the forma-

tion of bacterial vegetations on the valves — a more active inflammation (subacute bacterial endocarditis); (*d*) slow incomplete healing giving rise to deformed leaflets on which rheumatic inflammation is still recognizable; (*e*) complete healing resulting in thickened, stiffened valves with smooth surfaces.

As to pathogenesis, 76 hearts with old valvular defects are interpreted as follows: 55 from rheumatic endocarditis, 3 from bacterial endocarditis, 15 (all aortic stenosis of the calcified nodular type) of undetermined origin and 3 (pulmonary stenosis) congenital.

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DESCRIPTION OF PLATES

PLATES 33–40

PLATE 33

FIG. 1. 25–171. Acute rheumatic endocarditis. Ridge of small, firm vegetations near the edge on the auricular surfaces. Opacity of the leaflet above with prominent blood vessels and small hemorrhages.

FIG. 2. 22–28. Recurrent rheumatic endocarditis. Thickened leaflets with a ridge of very small vegetations near the edge on the auricular surfaces.

FIG. 3. 10–92. Early rheumatic lesion — area between vegetations. Endothelium intact, many large fibroblasts, a few lymphocytes and polymorphonuclears.

FIG. 4. 22–595. Early rheumatic vegetations. Closely packed fibroblasts. Abundant hyalin in one, a little in the other. A few polymorphonuclears and lymphocytes. Endothelium partly detached.

PLATE 34

FIG. 5. 22–185. Rheumatic endocarditis. The multicentric character of the lesion is shown. Platelet thrombi have formed where the hyalin has broken through the endothelium. Under the vegetations there is a diffuse inflammatory reaction — many small fibroblasts and extensive perivascular lymphocytic infiltration.

FIG. 6. 22–185. Small vegetation composed largely of hyalin.

FIG. 7. 18–204. Recurrent rheumatic endocarditis. A typical well formed fresh vegetation. Surface hyaline layer. Edema. Many fibroblasts. Central capillaries. The valve underneath shows scarring from a previous attack.

FIG. 8. 10–92. Acute rheumatic endocarditis. Detail of surface vegetation. Surface hyaline layer. Zone of large fibroblasts. Serous exudate.

PLATE 35

FIG. 9. 25–163a. Acute rheumatic endocarditis. Diffuse intense involvement of marginal part of leaflet. Hyaline layer on both surfaces. Numerous large fibroblasts.

FIG. 10. 25–163a. Higher magnification of an area of Fig. 9.

FIG. 11. 22–185. Acute rheumatic endocarditis. Cross-section of a leaflet showing hyalin in the central portion.

FIG. 12. 22–185. Acute rheumatic endocarditis. Section of valve above the level of the vegetations showing a diffuse proliferative inflammation. Large numbers of small fibroblasts. Prominent blood vessels. Some lymphocytes.

PLATE 36

FIG. 13. 25–631. Recurrent rheumatic endocarditis. Active vegetations on a thickened scarred valve. There is a little cellular exudate in the scar tissue underlying the vegetation.

FIG. 14. 24–364. Acute rheumatic endocarditis. Vegetation in stage of healing. Scar tissue with retrogressive changes in fibroblasts. Homogeneous hyaline layer at surface.

FIG. 15. 17–227. Recurrent rheumatic endocarditis. Healed vegetation. The surface hyaline layer of the vegetation blends with the hyaline fibrous tissue.

FIG. 16. 17–28. Subacute bacterial endocarditis. Bacterial emboli in capillaries surrounded by a zone of polymorphonuclears (embolic abscess).

PLATE 37

FIG. 17. 18–102. Subacute bacterial endocarditis. Proliferative inflammation within the valve. Large fresh soft thrombus with extensive deposits of calcium in its deeper part.

FIG. 18. 21–513. Subacute bacterial endocarditis. Proliferative inflammation. Large closely packed fibroblasts (some multinucleated). Very few collagenous fibers.

FIG. 19. 13–180. Subacute bacterial endocarditis; stage of healing. Hyaline thrombus; no organization. Valve largely converted into scar tissue.

PLATE 38

FIG. 20. 25–328. Old valvular defect with incomplete healing. Ridge of vegetations near the margin of the thickened leaflet. See Fig. 21 for microscopic structure.

FIG. 21. 25–328. Section through the ridge of vegetations shown in Fig. 20. Dense scar tissue underneath an old hyaline thrombus. Very little evidence of organization. This may represent a healed bacterial lesion.

FIG. 22. 16–185. Old valvular defect with incomplete healing. Large ulcers covered by thrombus. Small denuded areas near the free margin. See Fig. 23.

FIG. 23. Section of the large ulcer shown in Fig. 22. Hyaline thrombus; very little organization. Many leucocytes within the valve. Healing bacterial lesion.

PLATE 39

FIG. 24. 15–324. Old valvular defect with incomplete healing. Denuded areas on the thickened leaflets.

FIG. 25. 11–121. Old valvular defect with incomplete healing. Rheumatic vegetation with a dense connective tissue core. The surface hyaline layer is easily seen.

FIG. 26. 25–328. Section of a healed vegetation composed of scar tissue. The superficial hyalin is visible on the left side. No organization.

FIG. 27. 25–322. Old valvular defect with incomplete healing. Section through a raw area showing a thin layer of thrombus overlying dense fibrous tissue.

PLATE 40

FIG. 28. 20–250. Old valvular defect with incomplete healing. Old hyaline thrombus resting on hyaline scar tissue.

FIG. 29. 23–101. Old valvular defect with complete healing. Dense fibrous tissue in which a few capillaries are visible. A thin layer of hyalin at the surface suggesting the surface hyaline layer of a rheumatic vegetation.

FIG. 30. 25–82. Old valvular defect, calcified nodular type (Group 3). Aortic valve seen from above.

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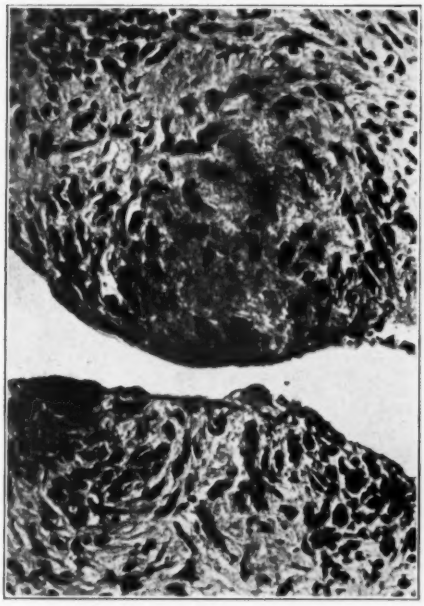

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Clawson, Bell and Hartzell

Valvular Diseases of the Heart

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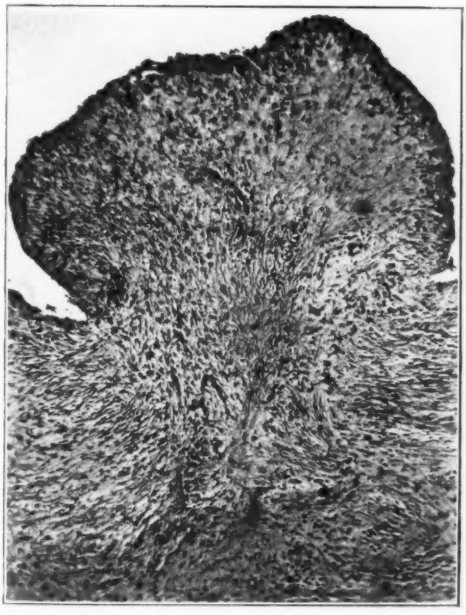

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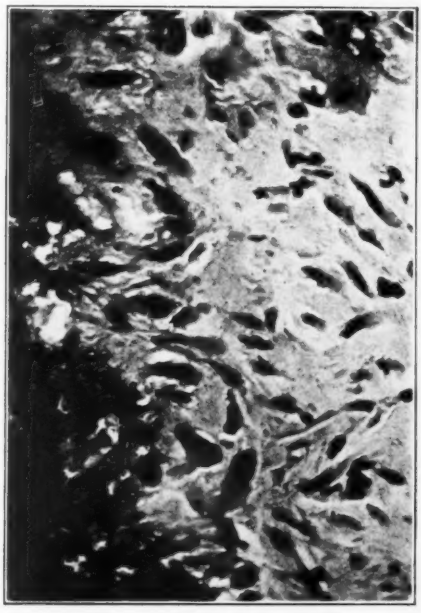

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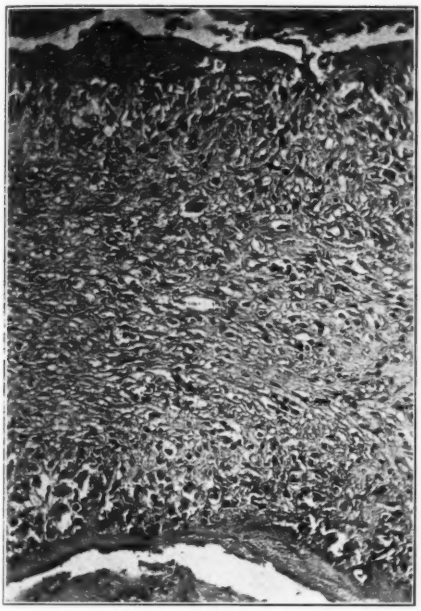
Valvular Diseases of the Heart



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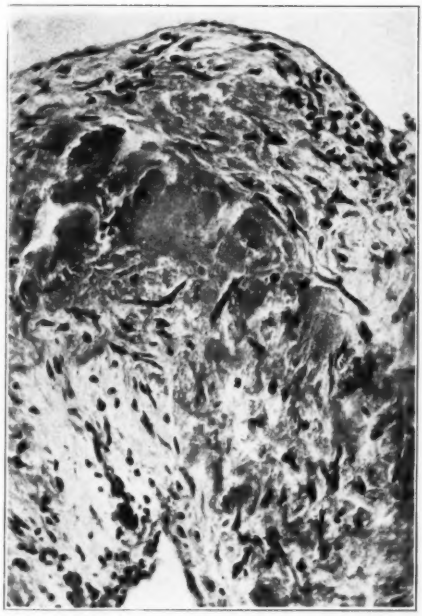

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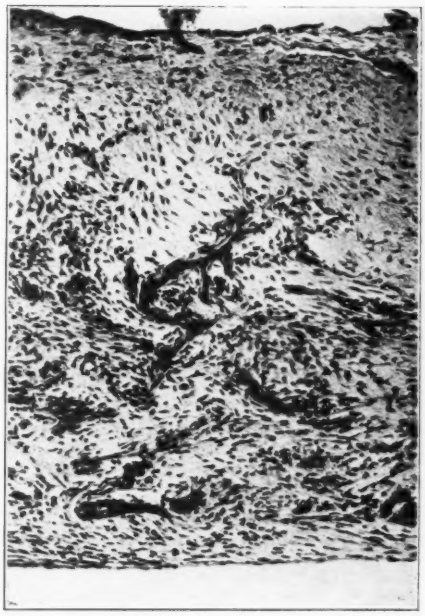

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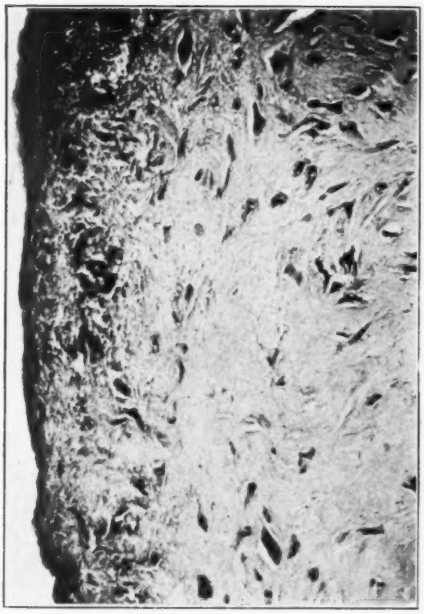

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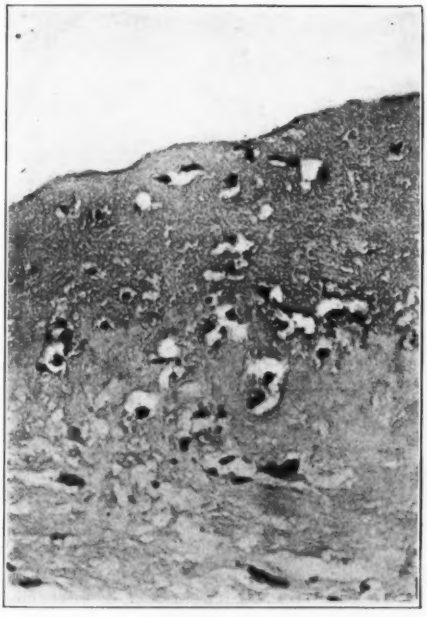

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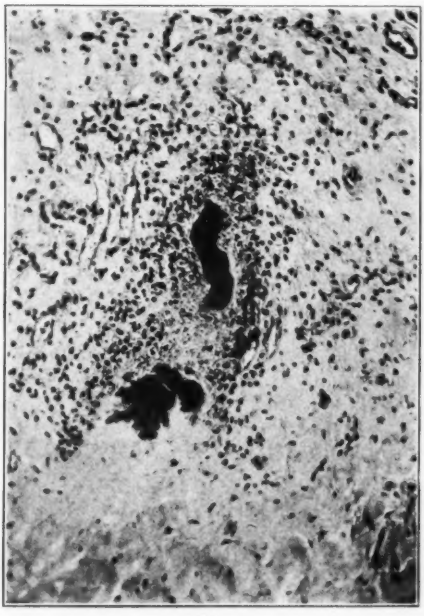

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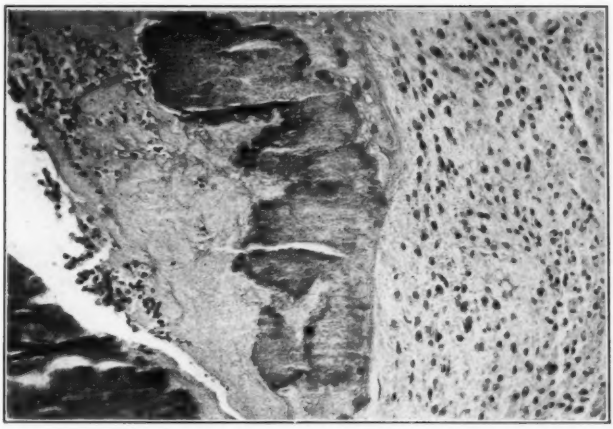

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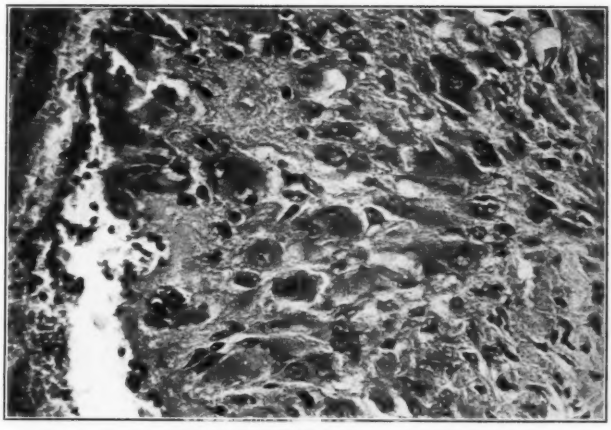

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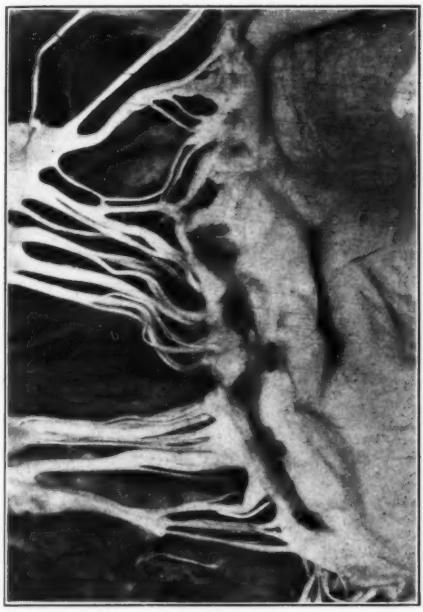

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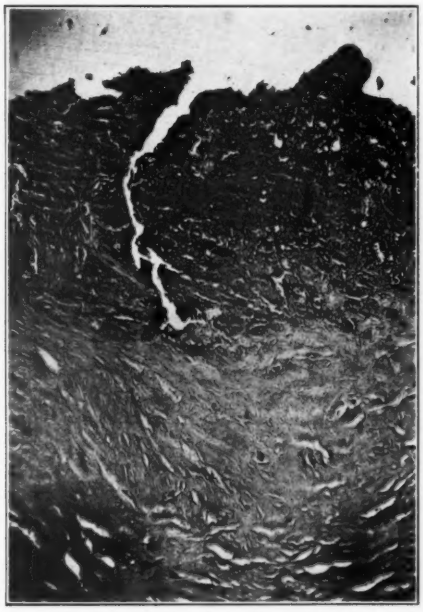

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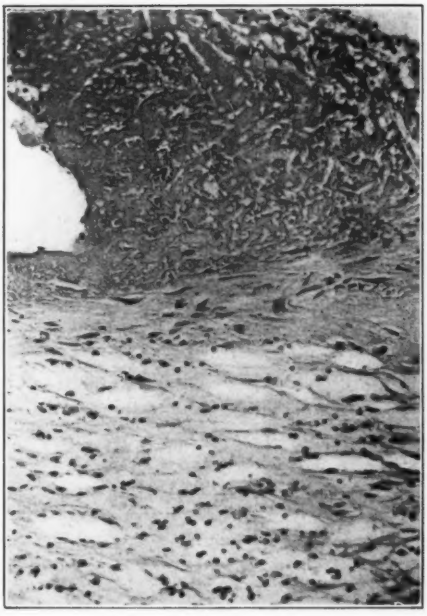

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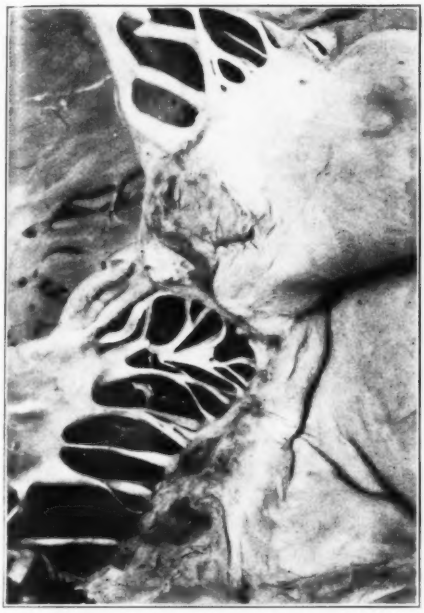
Clawson, Bell and Hartzell Valvular Diseases of the Heart



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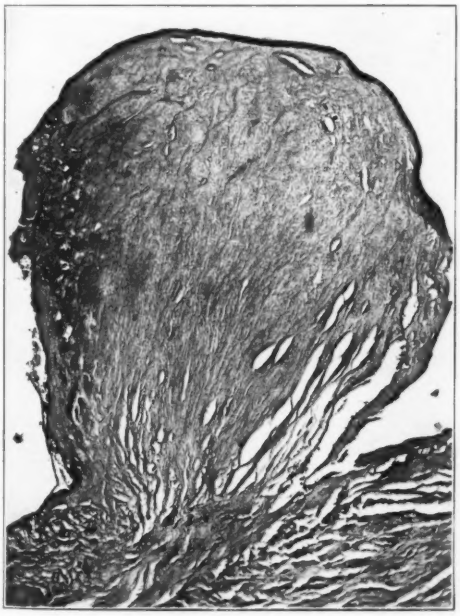

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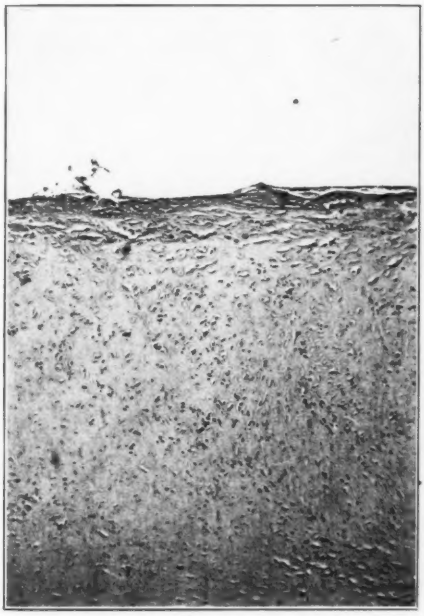

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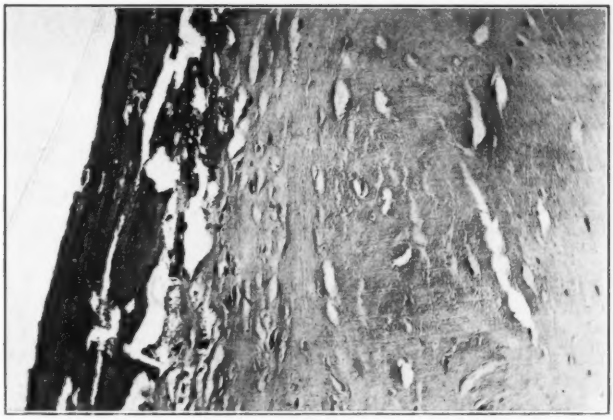
Clawson, Bell and Hartzell Valvular Diseases of the Heart



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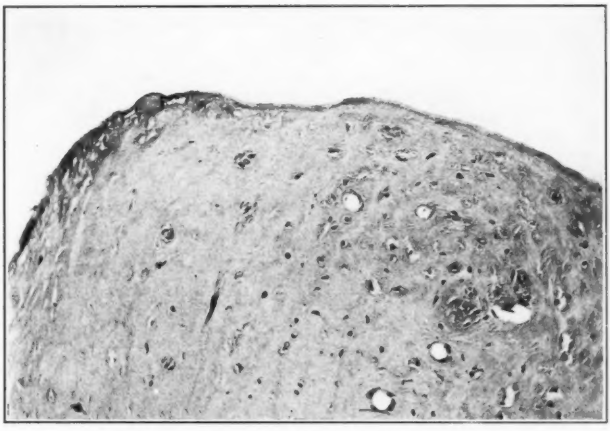

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SPECIFIC LESIONS OF PERIPHERAL BLOOD VESSELS IN RHEUMATISM *

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In the present uncertainty as to the causative agent of rheumatic fever, it is not possible to establish with finality the rheumatic nature of any given lesion. However, the frequent or constant association of a lesion with the clinical or pathologic features of rheumatic fever and its resemblance to other lesions generally recognized as associated with rheumatic infection, are presumptive evidence in favor of its rheumatic origin. Additional support is gained if the lesion in question has histologic features which are distinctive and which are not encountered in other known diseases. The specificity of the Aschoff nodule, indeed, of all rheumatic cardiac lesions, rests upon no firmer foundation than this.

That the virus of rheumatic fever may produce specific lesions of the aorta has been clearly shown.[1] It would not, therefore, be surprising to find that the smaller peripheral vessels should at times be the seat of rheumatic lesions. This in truth has proved to be the case.

A peculiar type of vascular inflammation has been found in a series of cases of rheumatic carditis, and in our experience in no other disease, so that we believe it to be specific and characteristic. We wish in this paper to describe the distinctive features of these lesions and to present detailed evidence in favor of their rheumatic origin. The material studied consists of a series of forty-seven consecutive cases of rheumatic heart disease, and of these the lesions were found in ten.

DISTRIBUTION OF THE LESIONS

The vascular changes to be described have thus far been found in the following situations: lungs, aortic valve, kidney, perirenal and periadrenal adipose tissue, appendix epiploica of the sigmoid colon, ovary, testis, pancreas and in a small polyp of the cecum. In most

* Received for publication April 7, 1926.

of these regions, only isolated vessels have been affected. As regards the lungs, however, two cases have been studied in which practically every small branch of the pulmonary arteries has been involved; in the kidney also the lesions have been quite widespread. The subcutaneous fat, joints and skeletal muscles have not been included in our routine material, so that we cannot speak of the possible occurrence of similar lesions in these tissues.

Histopathology of the Lesions

The alterations involve the entire thickness of the vessel wall and frequently, though not invariably, throughout its entire circumference.

The endothelium is swollen and basophilic, but appears intact. It may be exfoliated into the lumen (Fig. 1); this may in some instances take place after death while in other cases it is obviously lifted off by the accumulation of a coagulable exudate beneath it (Fig. 2). In no case has this alteration of the endothelium led to thrombus formation.

The wall of the vessel appears thick in comparison to the caliber of the lumen and this increase in thickness is particularly striking when only a portion of the circumference is affected. The thickening in the early phases of the lesions is due primarily to the infiltration of the vessel wall with fibrin (Fig. 3). This appears in the form of coarse interlacing strands staining pink with eosin, yellow with Van Gieson and blue with the Weigert fibrin stain. The fibrin threads in small vessels may extend into the contiguous cellular tissue, so that the original boundaries of the vessels are obscured (Fig. 4). In larger arteries the fibrinous exudate is often limited by the internal elastic lamella; in these cases, the threads are circumferentially disposed (Fig. 1).

Accompanying this deposition of fibrin, there occurs a necrosis of the cellular constituents of the vessel wall, as shown by the chromatin fragments scattered amongst the fibrin threads. In some vessels there is also extravasation of red blood cells, either immediately beneath the endothelium or in the meshes of the fibrin.

External to the necrotic wall of the vessel is a cellular tissue having a very distinctive and peculiar appearance (Fig. 5). It is composed of a loose fibrillar stroma, in part fibrinous, in which are many nuclei.

One may distinguish (1) lobed nuclei of polymorphonuclear neutrophiles, many of them pyknotic and fragmented, especially those nearest the vessel wall; (2) larger vesicular nuclei, staining less intensely than those of the polymorphonuclears and often distorted or compressed into bizarre elongate or club-shaped forms. They tend to be arranged radially. Still further out is a loose infiltration of lymphoid and plasma cells, occasional eosinophiles and young connective tissue cells. In this tissue are many dilated hyperemic capillaries, the largest often exceeding the diameter of the affected vessel. The zone of capillary distention frequently extends far beyond the area of cellular infiltration and is a constant and conspicuous feature of the early lesions (Fig. 10).

The behavior of the elastic fibers in the affected vessels can best be followed in serial sections. The earliest change noted in the internal elastic lamella is a swelling and partial alteration in the staining reaction, so that the fibers appear beaded and discontinuous (Fig. 1). As one follows the vessels into the region where there has occurred exudation of fibrin, the internal elastic lamella may become more difficult to distinguish (Fig. 11) and finally disappears altogether. Before this point is reached, one may observe that it has become greatly stretched and attenuated by the fibrin which has been deposited beneath the endothelium, and actual rupture often takes place, the ends becoming widely separated and everted. The gap between the ruptured ends is filled with a mass of fibrin.

The external elastic coat is even more difficult to trace, since in the small vessels affected it is often incompletely developed or even wanting. A few delicate fibrils persist and are pushed outward by the accumulated exudate (Fig. 11).

The recognition of a well formed wavy elastica interna, when the vessel is followed in series to a point where the injury is less severe, is evidence that the lesion may affect the small arterial branches.

In other instances, it is impossible even in serial sections to find any traces of an elastic coat, the thinness of the wall, as compared with the diameter of the lumen, indicating that the affected vessel is either a capillary or a precapillary venule.

Additional evidence that the lesion may affect capillaries was obtained in studying sections of an ovary. Here the vessel involved lay in the wall of a small cyst with the edema and cellular infiltration about it elevating the cyst wall into a rounded prominence which

projected into the cavity. When this vessel was followed in serial section, it could be traced directly into a sinusoidal capillary composed only of an endothelial lining with its basement membrane (Fig. 5). A similar observation was made in an affected capillary in the substance of the aortic valve.

It has been impossible to demonstrate bacteria in these lesions, either in the Gram-Weigert or methylene blue stained preparations.

In the larger arterioles of the lung the picture is slightly modified. The reactionary zone about the vessel is often inconspicuous or wanting, even when the infiltration of the media with polymorphonuclears is intense (Fig. 7).

Reparative Changes

The fibrinous exudate is gradually replaced by a permanent tissue. The fibrin filaments become swollen and fused into compact homogeneous masses which for a time retain the specific staining reaction. Isolated clumps of fibrin may be found even after the reparative process is well established.

Branching and polygonal cells with deeply staining vesicular nuclei, usually single but occasionally multiple (Fig. 11), appear amongst the fibrin threads. These we believe to be derived from the endothelium. Where there have been clefts or spaces left by the retraction of the fibrin, these cells tend to line them; and where extravasated red cells lie free in the meshes of the fibrin, the cells seem to encompass them and to establish new blood channels. There has never been observed any ingrowth of fibroblasts or newly formed capillaries from the adventitial tissue. This secondary vascularization of the intima is an amazing feature of the lesion. When fully developed, the original central lumen of the vessel which persists throughout, becomes surrounded by a spongy or vascular tissue composed of tensely congested, newly formed sinuses separated by a loose fibrous tissue. When followed in series, these newly formed channels are found to communicate in many situations with the original lumen on the one hand, and with collateral vessels on the other (Figs. 8 and 9).

The internal elastic lamella which has originally been displaced outwards by the exuded fibrin, may persist and may even become fortified by the development of a few fibrils which penetrate into the loose tissue between the newly formed sinuses.

While not frequently encountered, distended capillaries are occasionally seen lying between the internal and external elastic lamellae. These also may be followed through gaps in the internal elastic lamella to communicate with capillaries inside that layer.

The healed lesions thus resemble at first glance canalized thrombi. But it is clear when they are followed through their development that thrombosis does not occur at any stage. The resemblance is therefore only a superficial one. The fact that the circulation is at no time interrupted by thrombotic closure of the vessels explains the absence of infarcts in the lungs, even when the presence of an associated chronic passive congestion would favor their occurrence. Yet the interpolation of the cavernous tissue within the vascular tubes must bring about a slowing of the stream and probably results in stasis and congestion in the neighboring vascular channels.

The formation of new blood channels, as has been pointed out, seemingly depends upon an initial extravasation of red cells in the interstices between the fibrin strands. In some instances where this has not occurred, the development of new vessels fails to take place. In such a case, the exuded fibrin is gradually replaced by fibrillar connective tissue in which there eventually appear newly formed elastic fibrils. At this stage the picture simulates an obliterating endarteritis (Fig. 12).

The muscular coat in the larger arterioles is affected to a varying degree. In many instances, the muscle fibers virtually disappear, so that the internal elastic lamella when it has not undergone destruction comes to lie in close apposition to the elastica externa.

The fate of the peculiar inflammatory tissue which often forms a broad zone about the affected vessel is less easy to follow. Even in the more acute stages, many of the cellular components show degenerative changes, their nuclei being distorted and fragmented. Beyond that, it has not been possible to trace the process in detail. Presumably the wandering cells disappear. In our material there has not been observed, even in the healed lesion, great formation of scar tissue in the vicinity of the vessels.

Illustrative Cases

The following cases are chosen as exemplifying the lesions under discussion. A résumé of our material is given in abstract in Table I.

TABLE I

Autopsy no.	Age	Sex	Wassermann reaction	Rheumatic history			
				Tonsillitis	Arthritis	Cardiac	Chorea
9334	16	Male	0	+	–	+ Mitral stenosis and insufficiency	+ 10 years ago
9457	42	Female	0	–	+ "Growing pains" Polyarthritis, 3½ years ago	Heart trouble since childhood Mitral stenosis and insufficiency	–
9595	54	Female	0	–	–	Mitral stenosis and insufficiency Adherent pericardium	–
9626	33	Female	0	+	–	–	–
9627	9	Male	0	+	+ Frequent polyarthritis, first attack 4 years ago	Mitral stenosis Aortic insufficiency Pericarditis	–
9630	25	Male	0	+	+ Polyarthritis 2 years go	–	–
9636	47	Female	0	?	+ Polyarthritis First attack 10 years ago Admitted during second attack	+ Mitral insufficiency	–
9678	50	Male		?	+ Polyarthritis 10 and 3 years ago	+ Mitral stenosis	?
9680	9	Female		+	+ Polyarthritis 4 years ago	+ Mitral and aortic insufficiency	–
9691	68	Male	0	–	–	? Myocardial insufficiency	–

TABLE I

Lesions of rheumatic origin at necropsy	"Rheumatic" lesions of peripheral vessels	Other lesions	*Blood cultures*	
			Antemortem	Postmortem
Healed pericarditis Mitral stenosis	Pulmonary arterioles, acute and healing	Thrombus of right auricle Multiple infarcts of lungs Lobular pneumonia Fibrosis in lungs Chronic passive congestion of viscera	Negative (2)	Anhemolytic streptococcus (lung)
Mitral stenosis Rheumatic myocarditis (Aschoff bodies) Rheumatic aortitis	Bronchial and pulmonary arterioles, acute and healing Renal	Chronic passive congestion of viscera Myoma of uterus Hydrothorax Hydropericardium Ascites		
Adherent pericardium Rheumatic endocarditis, tricuspid, mitral and aortic valves Mitral stenosis Rheumatic myocarditis (Aschoff bodies)	Vessels about renal pelvis	Erysipelas Acute interstitial nephritis Acute splenic tumor Nodular cirrhosis of liver Lobular pneumonia Thrombi of left auricle	Negative	Negative
Rheumatic myocarditis (Aschoff bodies)	Ovarian Renal	Chronic nephritis Hypertrophy of heart		
Pericarditis Rheumatic endocarditis, mitral and aortic valves; left auricle Rheumatic myocarditis Rheumatic aortitis Aschoff bodies in diaphragm	Polyp of cecum	Chronic passive congestion of viscera Hydrothorax Ascites Polyp of cecum	Negative (3)	
Rheumatic endocarditis, mitral and tricuspid valves Myocardial fibrosis	Periadrenal fat	Lobar pneumonia Suppurative pleurisy	Pneumococcus I	
Rheumatic endocarditis, tricuspid, mitral and aortic valves Rheumatic pericarditis Rheumatic myocarditis (Aschoff bodies) Rheumatic aortitis	Perirenal fat Renal Aortic valve	Cholelithiasis Obsolete tuberculosis		
Rheumatic endocarditis, tricuspid, mitral and aortic valves Rheumatic myocarditis (Aschoff bodies) Rheumatic aortitis (Aschoff bodies)	Appendix epiploica of sigmoid	Thrombus of left auricular appendix Embolus of middle cerebral artery		
Rheumatic endocarditis (acute) Rheumatic myocarditis (Aschoff bodies) Rheumatic pericarditis	Perirenal fat	Subacute bacterial endocarditis Embolic nephritis Infarcts of spleen and kidneys		Anhemolytic streptococcus
Acute rheumatic myocarditis (Aschoff bodies)	Testis Pancreas	Thrombi of right auricle, and right and left ventricles Embolus of right internal carotid artery and right middle cerebral artery Infarct of brain		

CASE I. T. B., age 43, female (History No. 55714, Autopsy No. 9457, Dr. Butler). Admitted to Presbyterian Hospital in December 1922, and December 1923.

Past History. Acute rheumatic fever two and one-half years ago. Short of breath since childhood. Occasional precordial pain and palpitation for six years. No history of tonsillitis or chorea.

Present History. "Caught cold" four weeks before first admission. Fever, cough and malaise.

Physical Examination. Many coarse and fine râles in both lungs. Heart enlarged; soft systolic and a rough early diastolic murmur over entire precordium, loudest at apex. Pulmonic second sound accentuated. Liver edge 6 cm. below costal margin. Wassermann negative. Red blood cells, 3,500,000; white blood cells, 7,100; polymorphonuclear neutrophiles 86 per cent.

Discharged after three weeks with diagnosis of chronic bronchitis and chronic cardiac valvular disease (mitral stenosis and insufficiency).

Readmitted in December 1923, with history of bronchitis for ten days. Edema of legs.

Physical Examination. At that time, small areas of dullness and bronchial breath sounds near bases with coarse râles. Heart enlarged to right and left. Diastolic thrill at apex with systolic and diastolic shock. Rough rumbling diastolic murmur at apex and soft blowing systolic murmur, transmitted to axilla. Blood pressure 125 systolic and 68 diastolic. Lungs, dullness at apices with wheezing respiration. Small areas of dullness near bases with bronchial voice and diminished breath sounds. Coarse râles throughout lower two-thirds of both lungs. Liver edge 4 cm. below costal margin in midclavicular line. Shifting dullness in flanks with fluid wave. Extremities, marked edema of legs and ankles. Red blood cells, 3,600,000; hemoglobin, 80 per cent; white blood cells, 20,000; polymorphonuclear neutrophiles, 92 per cent.

Patient died on the second day after admission.

Clinical Diagnoses: Bronchopneumonia; chronic cardiac valvular disease (mitral stenosis and insufficiency); chronic bronchitis.

Necropsy. Anatomic Diagnoses: Chronic cardiac valvular disease, rheumatic (mitral stenosis); rheumatic myocarditis; cardiac hypertrophy and dilatation; hydropericardium; hydrothorax; ascites; edema of extremities; chronic passive congestion of viscera; acute arteritis, pulmonary arteries; fibromyoma of uterus.

Only the heart and lungs need to be described. The remaining viscera showed no lesions bearing upon the condition under discussion. Heart weighs 310 gm. Epicardium smooth. Right ventricle hypertrophied. Free edge of tricuspid valve thickened and opaque but without definite vegetations. Pulmonic valves normal. Left auricle dilated and hypertrophied. Auricular endocardium wrinkled above posterior leaflet. Mitral valve leaflets are shortened, thickened and calcified, projecting at right angles to blood stream. They are adherent to each other. Mitral orifice reduced to a buttonhole slit 14 mm. long. At two points the valve is ulcerated over calcium deposits. Chordae tendineae are thickened and shortened. Papillary muscles hypertrophied. Aortic cusps slightly thickened at their bases. Coronary arteries are normal. Myocardium shows no gross scarring.

Histologic Examination. Mitral valve: Greatly scarred with irregular hyaline masses of connective tissue and deposits of calcium. No bacteria are present in the Gram stain. *Myocardium:* Blocks from left ventricle are negative. A section taken through interventricular septum shows in the neighborhood of a

small coronary artery a few fusiform cells with vesicular nuclei, distinct nucleolus and purplish cytoplasm. There is fragmentation of collagen fibers in the vicinity of these cells. The appearances suggest a small Aschoff body. No scars are present. *Lungs:* Right lung weighs 500 gm. Lung is air-containing. On section it is reddish gray. Cut surface bathed in bloody fluid. Lower lobe contains numerous reddish areas which are relatively firm. Bronchial mucosa congested. Large branches of pulmonary artery project above cut surface. Alveolar septa thickened. No consolidation. Left lung weighs 400 gm. and presents same appearance.

Microscopic Examination. The most interesting changes are in the arterioles of microscopic dimensions. Practically no normal vessels are found. The lesions conform to those described and are illustrated in Figs. 2, 3, 7, 8, 9 and 12. All stages, from the subendothelial exudation of fibrin to final organization with development of new blood channels, may be seen.

There is no pneumonic exudate in the alveoli, but moderate edema and occasional fibrinous coagulum and desquamated cells are seen. There is congestion of the capillaries, but most intense about the affected arterioles. The pulmonary veins are normal.

The remaining viscera show only the changes of chronic passive congestion.

CASE II. E. H., age 47, female (History No. 62745, Autopsy No. 9636, Dr. Paige). Admitted to Presbyterian Hospital April 28, 1925, and died April 30, 1925.

Chief Complaints. Pain in left side for three weeks, multiple arthritis for two weeks, shortness of breath for ten years and hematuria for four days.

Past History. Acute rheumatic fever ten years ago. Increasing shortness of breath for three years. Influenza six months ago.

Present Illness. History vague and conflicting. The main points are (1) a known cardiac lesion; (2) polyarticular pain with fever for two weeks; (3) dyspnea; (4) hematuria for four days; (5) irregular menses; (6) headache. Has been irrational for three days.

Physical Examination. Obese woman, irrational. No petechiae. Suprasternal pulsation. Heart, considerably enlarged to left. Maximum impulse diffuse; heart sounds of fair quality, regular. Blowing systolic murmur heard over entire precordium, loudest over second right interspace. Blood pressure 170 systolic and 60 diastolic. Lungs dull at base; scattered moist râles. Abdomen, no masses felt. Right wrist somewhat reddened. No edema of extremities or clubbing of fingers. Red blood cells, 4,200,000; white blood cells, 24,800; polymorphonuclear neutrophiles, 90 per cent. Blood culture, sterile. Blood urea, 0.98 gm. per liter. Blood Wassermann, negative. *Urine:* specific gravity, 1.026; neutral; albumen, heavy trace; acetone present; many casts, epithelium and white blood cells; no red blood cells. Temperature 102.4 F; pulse 100; respiration 28.

Course. Eight hours after admission condition worse. Wildly irrational, then comatose. Râles in chest increased. Temperature gradually rose, death occurring in coma with temperature of 107.4 F.

Clinical Diagnoses: Acute rheumatic fever; chronic cardiac valvular disease (mitral insufficiency); cardiac hypertrophy; hypertension.

Necropsy. Anatomic Diagnoses: Rheumatic endocarditis (tricuspid, mitral and aortic valves); rheumatic pericarditis, fibrinous; acute rheumatic myocarditis; rheumatic aortitis; cardiac hypertrophy; chronic passive congestion of

liver, spleen and kidneys; edema of pia and lungs; focal necroses of liver; obsolete tuberculosis (right lung); cholelithiasis; melanosis of colon.

The lesions in this case bearing on the subject were in the heart and kidneys.

Heart weighs 500 gm. External surface and parietal pericardium covered with thick layer of fibrin, except over the posterior surface of the left ventricle. Many subepicardial hemorrhages. Myocardium pale and soft. No scars. Tricuspid valve irregularly thickened, with fusion of anterior and posterior leaflets. Pulmonic valve normal. Wrinkling of endocardium of left auricle above posterior leaflet of mitral valve. Mitral valve thickened, with tiny verrucae 1 to 2 mm. in size, of yellowish gray color along line of closure, and extending down to edge of valve and to insertion of chordae tendineae. Some of the chordae are slightly thickened. Papillary muscles hypertrophied. Aortic leaflets are thickened and have on them minute dull grayish yellow vegetations.

Histologic Examination. Recent fibrinous pericarditis without organization. Section of mitral valve shows characteristic rheumatic vegetations composed of hyaline material with ingrowing fibroblasts. Aortic valve also has characteristic vegetations; in its substance is a capillary, the wall of which is obscured by fibrinous infiltration. There is no great accumulation of cells about it.

Myocardium contains numerous Aschoff bodies and periarterial scars. (Culture of pericardial fluid sterile.)

Aorta in gross showed early atherosclerosis. Microscopically, there are scars about the nutrient vessels.

Kidneys, each weighs 110 gm. Identical in appearance. Normal on section save for congestion of vessels. Microscopically, no significant changes are found in the renal parenchyma. The arterioles and capillaries in the peripelvic fat and in the contiguous tissue of one kidney show an acute arteritis of the type described (see Figs. 4 and 10). There is necrosis and infiltration of all coats, but no suppurative changes. No thrombosis.

The viscera show no lesions of particular interest.

Discussion

One may advance the following arguments in favor of the rheumatic origin of these vascular lesions.

1. They have been invariably associated with undoubted cases of infection with the rheumatic virus and have not, in our experience, been found in any case which did not show rheumatic lesions.

2. The finer histologic features are in many respects analogous to those present in the rheumatic lesions of the left auricle, as described in the recent paper by VonGlahn.[2] Particularly in the reactive tissue about the vessels there is the same peculiar combination of elongate and distorted nuclei, eosinophiles and fragmented polymorphonuclears.

3. The lesions have a specific character and do not coincide with any hitherto well defined type of vascular disease. They perhaps most closely resemble those of periarteritis nodosa, but the following

differences may be noted: (*a*) In periarteritis nodosa, thrombosis is of frequent occurrence; this has not been seen in any instance in the rheumatic cases. (*b*) Periarteritis nodosa commonly affects arteries of medium caliber. In the cases above described the smaller arteries as well as those of medium caliber, arterioles and sinusoidal capillaries have been affected. (*c*) The inflammatory changes in periarteritis nodosa lead, as the name indicates, to nodule formation often of macroscopic dimension and frequently to the development of aneurysm and infarcts. The "rheumatic" lesions are not nodular and invariably are microscopic. Though the affected vessel may show slight dilatation, this is never sufficiently localized or sufficiently marked to justify description as an aneurysm. Nor, for the reason already discussed, do the "rheumatic" lesions lead to infarction or hemorrhages from rupture. The cellular components of the reactive tissue differ from those in periarteritis nodosa. In the rheumatic lesions, eosinophiles are not abundant; in periarteritis nodosa they are often the most conspicuous cellular element. Plasma cells also are not numerous in the rheumatic lesions; they are of frequent occurrence in the other.

The lesions bear even less resemblance to those occurring in the course of acute pyogenic infections. The absence of bacteria, of thrombus formation and of a typical suppurative reaction is sufficient to exclude vascular lesions of this category.

Review of Literature

It is most interesting that a localization of the rheumatic virus in peripheral vessels should have been surmised for many years. The term "rheumatic arteritis" dates back to the well known treatise of Bouillaud (1840),[3] and clinical cases purporting to illustrate this condition have been cited by Lemaire (1864),[4] Fernet (1865),[5] de Fajole (1866),[6] Lelong (1869),[7] Lecorché (1869),[8] Guéneau de Mussy (1874),[9] Legroux (1884),[10] Huchard (1892),[11] Hanot (1894),[12] Brault (1896),[13] Astier (1897),[14] Blot (1898),[15] Besson (1900),[16] Barié (1905, 1913) [17] and Queuille (1906).[18] In spite of their suggestive titles, little definite information can be extracted from these papers. For the most part, they are reports of clinical cases in which violent pulsation of the larger peripheral arteries attracted attention. The few necropsy reports and the still rarer histologic descriptions of the

larger vessels are too indefinite to justify analysis. A good summary of the French literature is to be found in the paper of Barié (loc. cit. 1913).

A few references, equally indefinite, are to be found in the German literature. Thus Wiesel and Löwy (1919) [19] in a paper upon the effects of acute and chronic circulatory insufficiency upon peripheral blood vessels, made the following statement (p. 1085): "Acute rheumatic fever likewise is accompanied not only by endocardial, but also by arterial lesions." * No specific changes are described. In a recent paper (1923), Wiesel [20] again alludes to the effect of rheumatism, as well as other infectious diseases, upon the peripheral arteries. Here he mentions changes in the media as a factor leading to juvenile arteriosclerosis. Fahr (1920) [21] is inclined to attribute to rheumatism, in addition to lues and lead, etiologic importance in the production of "malignant sclerosis" of the kidney. He cites five cases in which renal disease followed at varying intervals a rheumatic infection. No reference is made to distinctive vascular lesions. In a subsequent paper (1921),[22] Fahr again refers to rheumatic affections of the small renal arteries as a probable cause of malignant renal sclerosis. This paper contains a low-power photomicrograph of periarterial granulomatus formation with lymphoid cells, fibroblasts and occasional eosinophiles. The details are difficult to distinguish, but it is possible that the lesion pictured is identical with that described by us.

In the English and American literature no definite allusions to rheumatic arteritis have been found. However, it is not surprising to discover that Mallory,[23] who has interested himself particularly in infectious lesions of blood vessels, should have given in his textbook a most accurate reproduction of the type of lesion under discussion. The vessel involved was situated in the kidney, but there is nothing in the legend or text to indicate whether or not the case was one of rheumatic fever.

Ophüls,[24] in his discussion of the etiology of periarteritis nodosa, emphasizes the apparent close relationship between this disease and the "ill-defined group of subacute and chronic 'septic' conditions, with so-called rheumatic symptoms, and frequently associated with endocarditis." While it is possible that certain cases of rheumatic vascular disease may have been interpreted as periarteritis nodosa,

* "Auch die akute Gelenksrheumatismus ist . . . nicht nur von Erkrankungen des Endokards, sondern ebenso von solchen der Arterien begleitet."

there are, as has been pointed out, very clear-cut differential features. The final decision as to whether these two somewhat similar conditions are related, must be deferred until the cause of each is known.*

Conclusions

In a series of forty-seven consecutive cases of rheumatic cardiac disease, specific lesions of the small peripheral arterioles and capillaries, either systemic or pulmonary, have been found in ten.

These lesions are characterized by the exudation of fibrin into and about the vessel, by destructive changes in the cellular components of the vessel wall, by a distinctive cellular reaction in the adjacent tissue and by the absence of thrombosis.

These acute lesions are followed by organization with or without formation of new collateral channels within the thickened intima and occasionally within the muscular layer.

We wish to express our thanks to Doctor Walter W. Palmer for permission to use the clinical records, and to Mr. Alfred Feinberg and Miss Madeline Chickering for the drawings.

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* There has come to our attention since this paper was submitted for publication, an article by Baehr and Sacks (*Proc. New York Path. Soc.*, 1923, xxiii, 64). They described vascular lesions of the renal arterioles in cases of glomerulonephritis associated with verrucous endocarditis, three of which were regarded as typically rheumatic, and two as belonging to the "atypical form" described by Libman and Sacks.

In the mildest form of involvement, the changes . . . "consisted of endothelial swelling and proliferation. In the more severely damaged arterioles, there was irregular hyaline degeneration and necrosis of the normal elements of the vessel wall, with karyorrhexis of many of the nuclei, infiltration at times with polymorphonuclear and round cells, and the deposition of fibrin and blood platelet thrombi in the lumen. These changes were often limited to the vasa afferentia close to the pedicle of the glomerulus; in other instances they extended as far as the terminal segments of the interlobular arteries. Some of the arterioles showed thrombus deposition with comparatively little inflammatory change in the vessel wall."

The authors are undecided whether these cases constitute a specific infection with an endotheliotropic virus, unusual forms of rheumatic fever or are related to the atypical group of endocarditis of Libman and Sacks.

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DESCRIPTION OF PLATES

Plates 41–46

Fig. 1. Autopsy No. 9680. Arteriole in fat near pelvis of kidney. Exfoliation of endothelium and necrosis of vessel wall with fibrinous exudation. Marked inflammatory reaction in adjacent tissue. Congestion of surrounding capillaries. (Hematoxylin-eosin stain.)

Fig. 2. Autopsy No. 9457. Pulmonary arteriole. Fibrinous exudate beneath endothelium. Stretching and beginning fragmentation of internal elastic lamella. Thinning of muscular coat. Slight inflammatory reaction in surrounding tissue. No thrombus formation. (Weigert's elastic tissue-hematoxylin-eosin stain.)

FIG. 3. Autopsy No. 9457. Pulmonary arteriole. Dense accumulation of fibrin beneath endothelium with small masses in muscular coat. (Gram-Weigert-safranin stain.)

FIG. 4. Autopsy No. 9636. Arteriole in column of Bertini of kidney. Fibrin beneath endothelium, in vessel wall and ramifying into surrounding tissue. (Gram-Weigert-safranin stain.)

FIG. 5. Autopsy No. 9626. Sinusoidal capillary in wall of ovarian cyst. Necrosis of vessel wall with fibrinous exudate. Peculiar type of avascular inflammatory tissue surrounding the vessel. (Hematoxylin-eosin stain.)

FIG. 6. Inflammatory tissue in wall of left auricle in rheumatic endocarditis. (Reproduced from "Endocarditis of rheumatic origin," VonGlahn, Fig. 10, Am. J. Path., 1926, ii, 1.) Compare character of cell reaction with that shown in Fig. 5.

FIG. 7. Autopsy No. 9457. Pulmonary arteriole. Acute lesion in cross-section and healing state in portion of vessel cut longitudinally. Zone of capillary congestion about affected vessel. (Wiegert's elastic tissue-hematoxylin-eosin stain.)

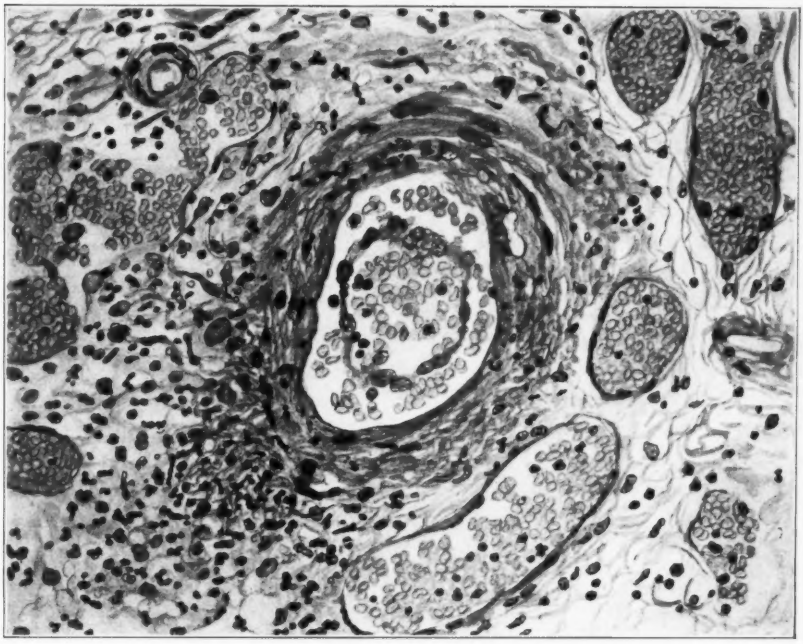
FIG. 8. Autopsy No. 9457. Pulmonary arteriole. Late stage, longitudinal section of vessel. Lumen occupied by distended capillaries surrounded by loose connective tissue. The elastic lamella has remained intact. (Weigert's elastic tissue-hematoxylin-eosin stain.)

FIG. 9. Autopsy No. 9457. Pulmonary arteriole. Cross-section. Changes same as in Fig. 8. (Weigert's elastic tissue-hematoxylin-eosin stain.)

FIG. 10. Autopsy No. 9636. Arteriole in column of Bertini of kidney. Necrosis of vessel wall with fibrinous exudate. Necrosis of elastic lamella. Note zone of capillary congestion about affected vessel. (Weigert's elastic tissue-hematoxylin-eosin stain.) Same vessel as shown in Fig. 4.

FIG. 11. Autopsy No. 9691. Arteriole in testis with internal elastic lamella almost completely destroyed. A portion of it persists immediately near upper margin of original lumen. Another fragment is seen below separated from lumen by large mass of fibrin; a few fragments remain also of the external elastic lamella. The fibrinous mass contains a number of large basophilic branching cells with one or several nuclei. There is also a newly formed blood channel. Lesion shows repair. (Weigert's elastic tissue-hematoxylin-eosin stain.)

FIG. 12. Autopsy No. 9457. Pulmonary arteriole. Healed stage without vascularization of fibrinous exudate. In this stage the vessel presents the picture of obliterating endarteritis. Two fragments of the internal elastic lamella are shown marking the limits of the original intima. (Hematoxylin-eosin stain.)



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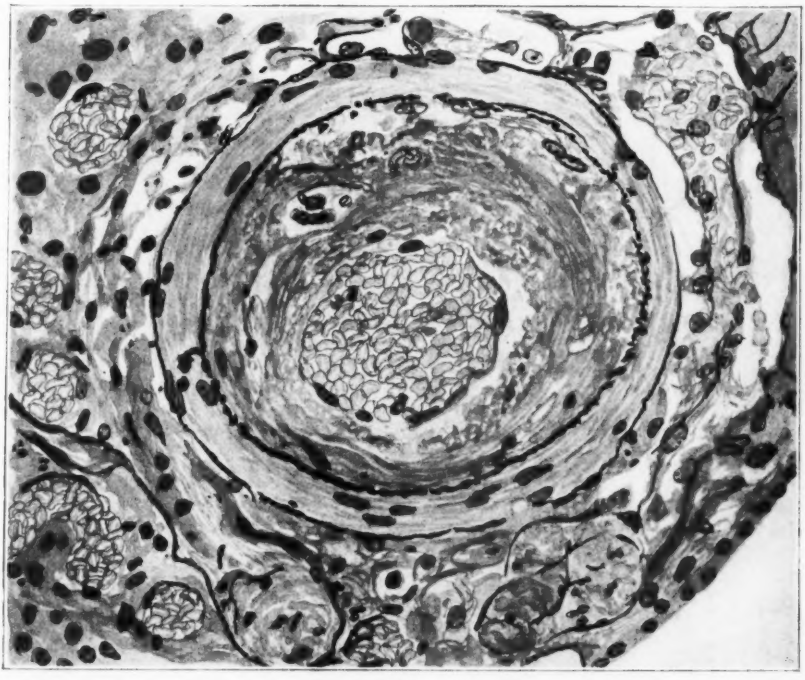

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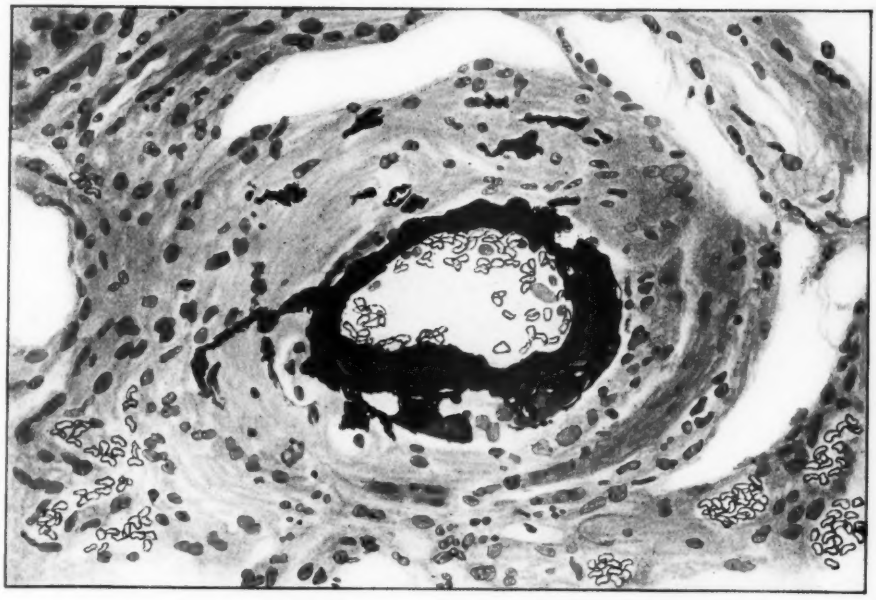
VonGlahn and Pappenheimer Lesions of Blood Vessels in Rheumatism



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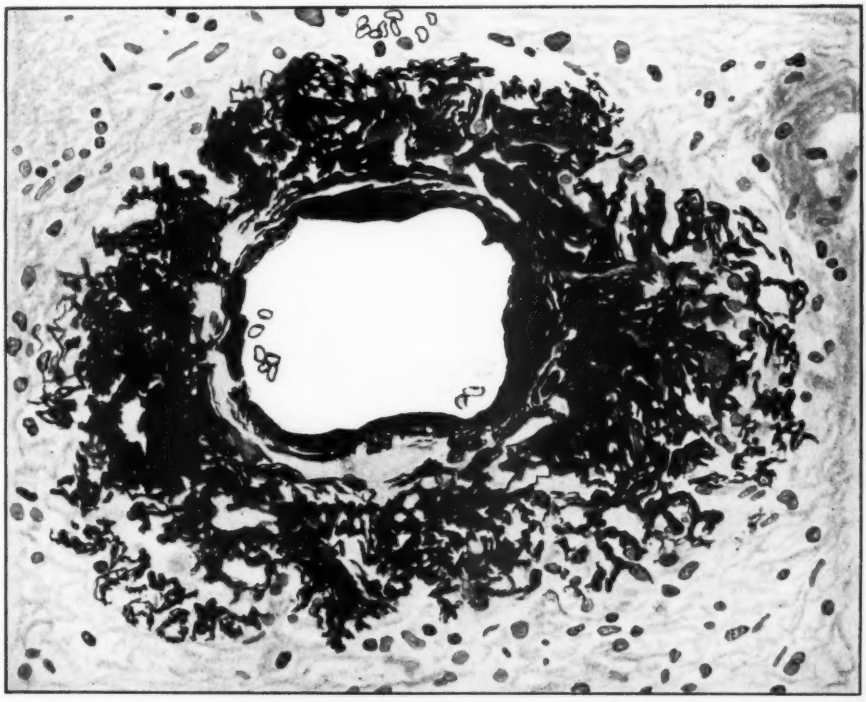

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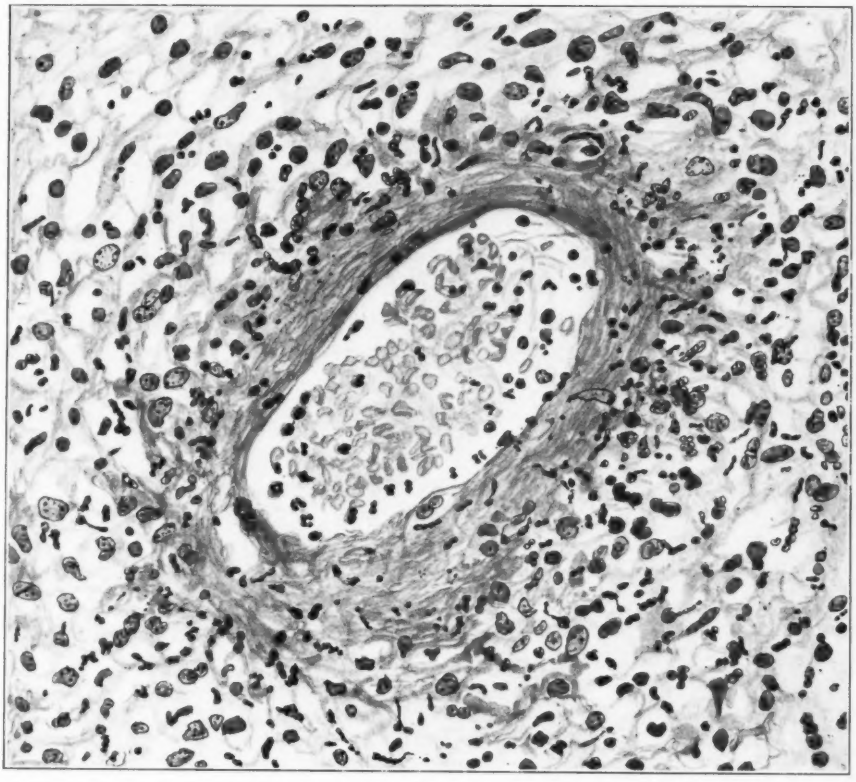

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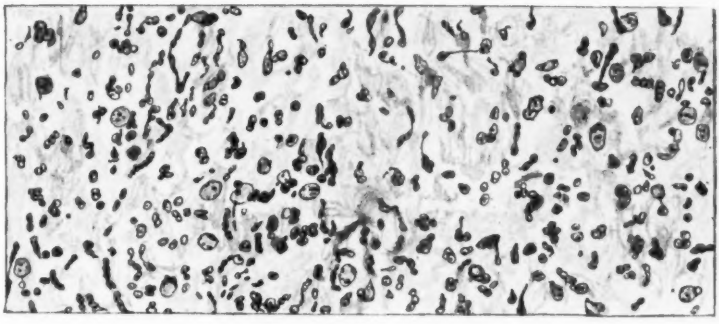

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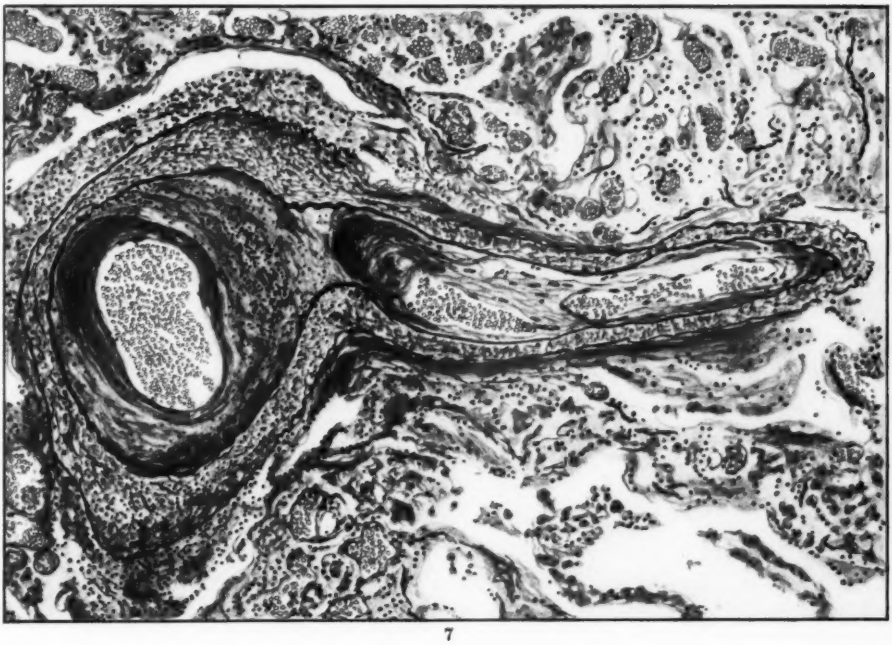

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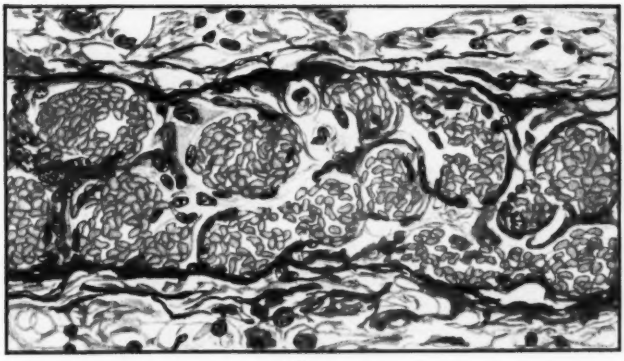

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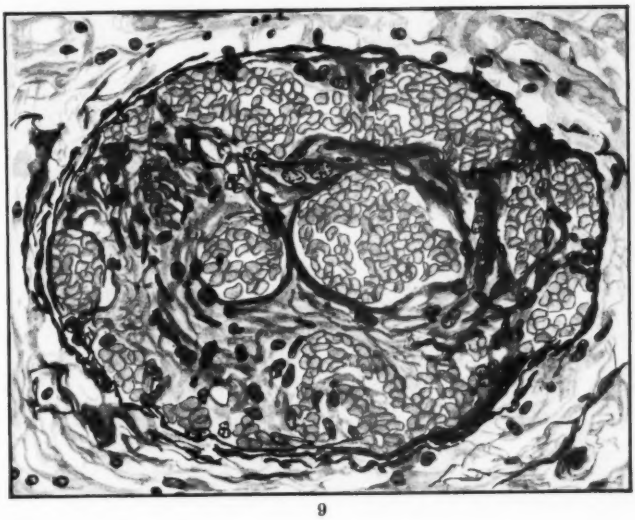

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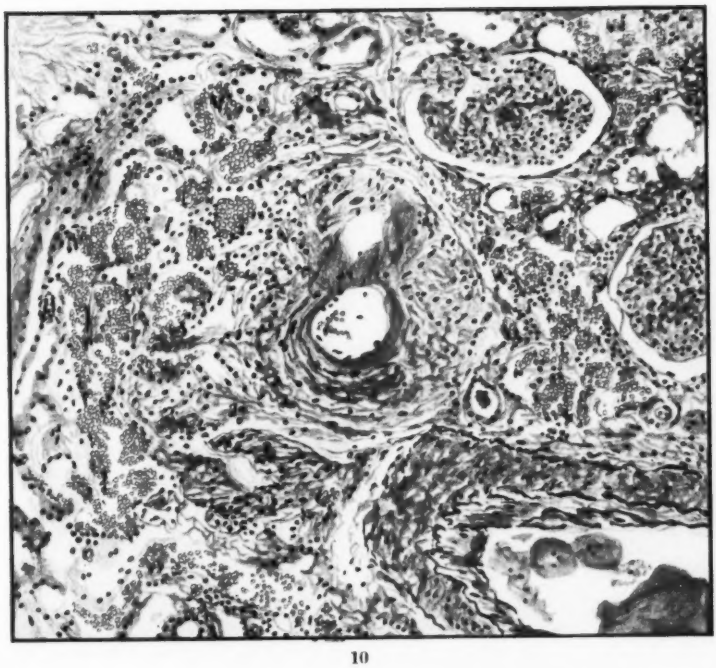

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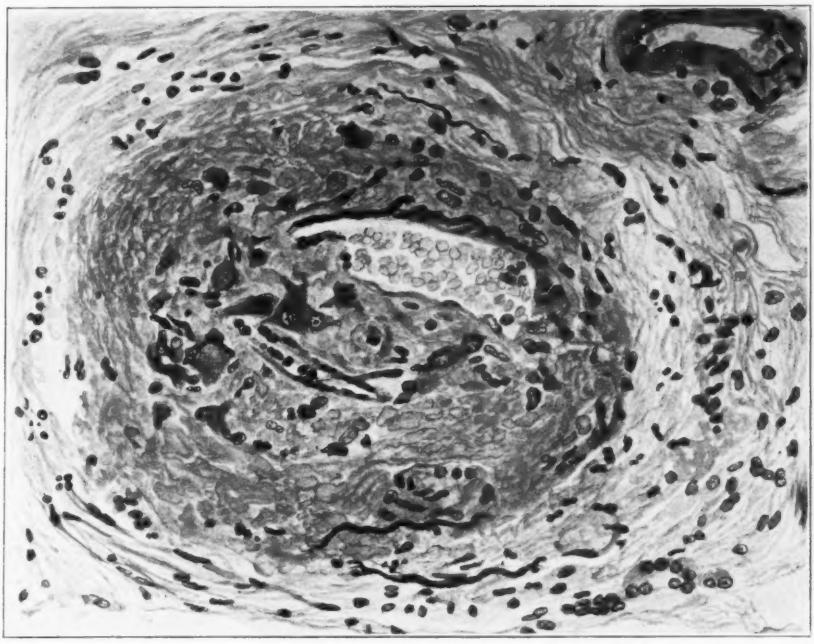

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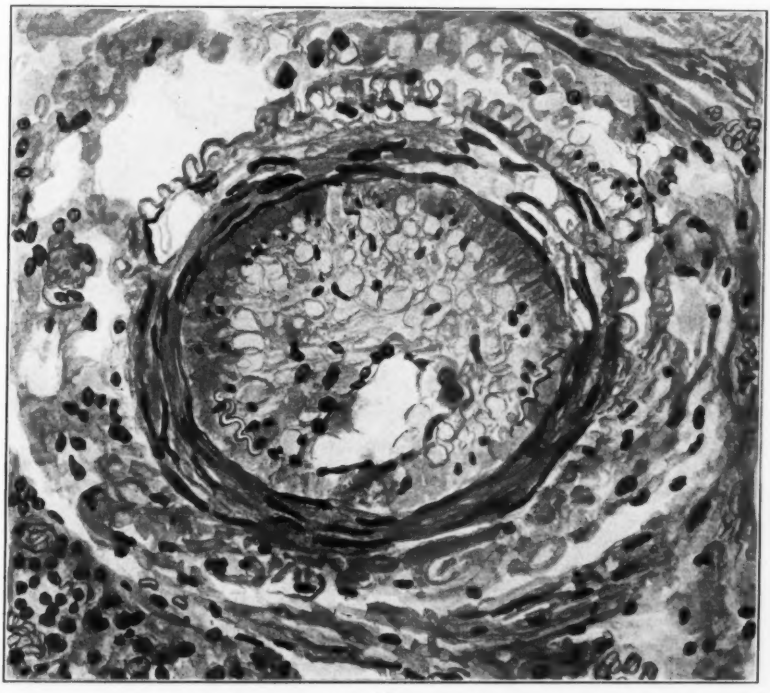

12

VonGlahn and Pappenheimer Lesions of Blood Vessels in Rheumatism

A CASE OF ADIPOSIS DOLOROSA WITH NECROPSY *

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Introduction

Adiposis dolorosa, first described by Dercum,[1] is characterized by the following syndrome: (1) great and localized adiposity with tenderness to pressure over the fat pads and along the course of nerves, occasionally with pain and aching in the extremities; (2) marked asthenia, or fatigability; (3) psychoses and epileptiform seizures; and (4) bullae or ulcers on the extremities. Subnormal temperature, decreased metabolic rate and a tendency toward hemorrhage may also be present. The disease is characterized pathologically by changes in the endocrine organs, such as sclerosis with atrophy in some instances and hypertrophy in others. There is much to indicate that the primary lesion is situated in the hypophysis cerebri, the other changes occurring consequently, but the character of this lesion is very variable, as will be seen presently.

The case we are reporting fulfills the above criteria, but as there is no manifest history of tenderness over the fat masses we may be criticized for including it in the category of painful adiposity. It is, however, not improbable that the patient might have admitted tenderness over the masses had we been able to question her on that subject and it is our impression that this symptom, during life, is of far less importance than the conformity of the pathologic findings in the case to those previously described.

Winkelman and Eckel[2] recently reported an instance of this disease, with necropsy, and here the reader may find a complete synopsis of the fifteen cases reported prior to theirs, as well as a list of references. Although some two hundred clinical reports have been made, only sixteen necropsies appear in the literature. Winkelman and Eckel review the subject as follows.

On reviewing the necropsy findings of the fifteen cases in the literature, one is impressed by the pluriglandular involvement in most of the cases. In only

* Received for publication March 8, 1926

two cases were there no definite changes in the ductless glands (Rome and Falta). Of the eleven patients in whom the pituitary body was examined, eight showed definite alterations; the thyroid was abnormal in twelve cases; the sex glands were pathologic in nine; the suprarenal in three; and the pancreas in two. Our own case showed pituitary, suprarenal and ovarian pathologic changes. It is of interest from a clinical standpoint, to note that the condition is five times more prevalent in the female and that most cases develop after the age of 35.

The changes in the pituitary gland, as summarized in this review, vary from slight lymphocytic infiltration to adenomatous hyperplasia, or to malignant transformations constituting actual adenocarcinoma, or resembling it. One glioma is recorded. There is, then, no typical pituitary lesion. The usual change in the thyroid is sclerosis, with or without calcification and colloid retention. The suprarenals showed unilateral hyperplasia or adenoma in three instances. The gonads were listed as atrophic, sclerotic or "defective" in the nine reports mentioning them. Sclerosis and fatty invasion of the pancreas were noted in a few instances. Having stated the general characteristics of this disorder, let us proceed to the description of our case.

Clinical History

Present Illness. Ida F., 60 years of age, colored, single and a cook by occupation, was admitted to the medical service of the Cincinnati General Hospital on the evening of December 30, 1925. As she was irrational, non-coöperative and excited and as she died on the following afternoon, it was impossible to procure a connected history or to make a satisfactory examination of the patient. She had been an inmate of the Hamilton County Home for about two and a half years and had been granted leave to spend the Christmas holidays with friends in Cincinnati. While in apparently good health, she suddenly had a "stroke" which, so far as can be ascertained, consisted of a state of unconsciousness of unknown duration. Since then she seemed "out of her head" and was brought to the hospital the day following her seizure.

Past History. Only one fact seems fairly certain: she had been fat all her life, a childhood friend stating that she weighed over 200 lbs. when only 18 years old. She suffered from no severe illnesses and was always up and about, although recently inconvenienced by leg ulcers, shortness of breath and asthenia. While walking outdoors, she would frequently be forced to sit down on a door step and catch her breath and rest before being able to proceed. While at the Home she could always care for herself and at no time had anyone heard her complain that her fat was painful.

Family History. Her parentage was obscure; she seems to have had no brothers or sisters and was reared by an aunt who was likewise "very heavy."

Physical Examination. This was very unsatisfactory on account of the patient's mental condition and her extreme obesity. The positive findings include large, equal and fixed pupils and a bitten, bleeding tongue-tip held be-

tween a toothless upper gum and a few worn, carious lower teeth. Percussing the chest, and locating the point of maximum impulse and relative cardiac dullness were equally unsatisfactory and uninstructive, on account of the heavy layers of fat over the chest. Besides labored breathing, auscultation revealed muffled, rather harsh and prolonged expiratory sounds. The faint, irregular heart sounds presented many extra systoles; the blood pressure did not register and the radial pulse was impalpable. Varicose ulcers were on both legs.

Laboratory Data. Temperature, 97 F; pulse, 96 (?); and respiration 28. Blood: erythrocytes normal and leucocytes 15,500 per c. mm. A differential count showed: neutrophiles 68 per cent; eosinophiles 0 per cent; basophiles 1 per cent; lymphocytes 30 per cent; large mononuclears and transitionals 1 per cent. Blood chemistry: sugar, 165 mgm.; urea nitrogen, 34 mgm.; and alkaline reserve, 42. Wassermann, negative.

Urine: A catheterized specimen was amber, clear and acid to methyl red; albumin, +++; sugar, positive; acetone, negative; blood (by Meyer's test), ++++. Several hyaline and granular casts, a few leucocytes and erythrocytes were found in the sediment.

Course in Hospital. Until she died, less than a day after admission, the patient had six convulsions, lasting from two to five minutes and preceded by a peculiar outcry. The whole body was equally involved, first in a short tonic, then in a clonic spasm lasting two to three minutes and followed by a gradual relaxation. During the latter part of each seizure and just afterward, she frothed at the mouth. During the day Cheyne-Stokes respiration set in and slight right-sided facial weakness was noted, although the extremities were not involved.

Clinical Diagnoses: Uremia, cerebral hemorrhage (?), auricular fibrillation and adiposis dolorosa.

Necropsy Protocol

Anatomic Diagnoses: Adiposis dolorosa. Bilateral suprarenal adenomas and softening, thyroid hyperplasia and sclerosis, persistent thymic tissue, atrophy and fatty invasion of pancreas, atrophy of the ovaries and adenomatous hyperplasia and sclerosis of the hypophysis with widened sella turcica. Exostoses of the inner table of the skull, tumors of the dura, cerebral atrophy and increased cerebrospinal fluid.

Cardiac hypertophy and dilatation, fatty infiltration of the myocardium with myocardial degeneration, fatty invasion from the epicardium. Atheroma of aorta and arteriosclerosis. Hypostatic pulmonary congestion. Atrophy and fibrosis of the spleen. Fatty invasion and passive congestion of the liver and cholelithiasis. Chronic vascular and glomerulonephritis. Fibrosis of the uterus and uterine polyp. Umbilical hernia. Ulcers of both legs above the ankle. Dental caries and pyorrhea alveolaris.

Cause of Death: Uremia and cardiac failure from decompensation.

DESCRIPTION OF NECROPSY

The body is that of an extraordinarily adipose negress (Fig. 1), measuring 161 cm. in length and weighing approximately 350 lbs. (77 kgm.). Rigor mortis is marked in the extremities and the lower jaw; no postmortem lividity can be determined. The fat is apparently subcutaneous and is deposited in huge accumulations over the abdomen, shoulders, chest, upper arm and thighs; while the head, forearms and hands and the lower legs and feet are of normal size and free from it. A thin, brownish fluid escapes from the mouth; the lips are cyanotic. The pupils are equal and about 4 mm. in diameter, with marked arcus senilis of the irides. The right radius exhibits a knob-like protuberance over the inner distal extremity, suggesting an old, healed fracture. There is a delicate grayish blue striation of the skin over the flanks (striae atrophicae) and glazed and thickened skin (intertrigo) over the apposed surface of the apron-like abdominal fat pad and that of the thighs, more than halfway to the knees. The fatty deposits are quite symmetrically distributed in every instance. Ulcers present over the inner surface of both shins, just above the ankle; that on the right measures 9.5 × 2 cm. and that on the left 2.5 × 3 cm. The surrounding skin is atrophic, scarred and shows varicosities; the ulcers are covered by apparently healthy granulations.

Body Measurements

	In circumference		In circumference
Head	57.0 cm.	Waist	142 cm.
Upper arm	58.0 cm. each	Hips	150 cm.
Forearm	right, 36.5 cm.	Thigh	right, 85 cm.
	left, 38.0 cm.		left, 90 cm.
Wrist	right, 21.0 cm.	Knee	51.5 cm. each
	left, 20.0 cm.	Calf	right, 45 cm.
Chest	125 cm.		left, 46 cm.
Bust	143 cm.	Ankle	25 cm. each

	Thickness	Length	Width
Hands	5 cm.	17.5 cm.	Average, 11 cm.
Feet	7 cm.	26.0 cm.	10 cm.

Iliac crest to knee	54.5 cm. on each side
Knee to internal malleolus	39.0 cm. on each side
Length of arm	40 cm. each
Length of forearm	30 cm. each

The primary incision reveals a thick layer of subcutaneous fat averaging 70 mm. in thickness over the chest and 162 mm. over the abdomen. The omentum is moderately adipose and the mesenteric vessels are embedded in lines of fatty tissue. The liver presents 4 cm. below the costal margin. A hernia, 3 cm. to the right of the umbilicus and 2 cm. above it, contains about 6 cm. of the transverse colon. Upon removing the sternum a fatty mass shot with smaller glandular masses and measuring 7.5 × 5 × 2 cm. is exposed, overlying the upper portion of the pericardium and occupying the site of the thymus. It weighs 40 gm. The heart weighs 605 gm. and is enveloped by a very adipose pericardium. The aorta shows the usual changes seen in atheroma of a non-specific type. The thyroid is rather large, globular and of a uniform reddish color; on section, the knife meets with considerable resistance and the colloid content is somewhat diminished.

Of the other organs, we shall mention only the following. The pancreas is superficially normal, but on section it proves to be congested, finely granular, soft and friable and somewhat invaded by fatty tissue. The suprarenals show postmortem softening and each contains a spheroidal mass of what appears to be cortical substance in the form of an adenoma; each mass measures about 1.5 cm. in diameter. These glands are soft and fleshy. The kidneys weigh 340 gm. together and show the typical changes of chronic vascular and glomerulonephritis. The ovaries are small and sclerotic.

The findings in the head require special consideration. Upon opening the calvarium, it is found to be from 0.5 to 1 cm. thick and rather compact. It presents a peculiar thickening of the inner table in the right parietal region in the form of thin, flat exostoses several centimeters long and one or two centimeters wide which are raised but a millimeter or so above the general level of the bone and form a roughly hand-shaped excrescence, the fingers splayed forward. There is a knob-like exostosis over the inner end of either petrous bone, near the attachment of the tentorium. The dura is thick and tough, but not remarkable, except for the presence of a nodular mass of firm, grayish tissue 0.5 cm. in diameter over the left tentorial margin.

The brain weighs 1115 gm., is shriveled and does not take up all the room allowed it by the cranial cavity, appearing to be definitely atrophic. The sulci are deep and wide and the convolutions nar-

row. An increased amount of cerebrospinal fluid escapes from the meninges. Over the right parietal convexity, in the region of the post-central sulcus, is a pyramidal depression, 4 × 2.5 × 2 cm. in size; section of this area reveals nothing but atrophy to account for the condition, but it underlies the exostoses already described. Careful examination of the hemispheres and basal ganglia reveals nothing of note; no definite areas of hemorrhage are encountered.

The pituitary body weighs 1 gm., and measures 17 mm. in length, 15 mm. in width and 7 mm. in thickness; the anterior lobe is large, yellow and tough and is asymmetrical, surrounding the pars posterior and extending higher on the right than on the left. The posterior lobe, while somewhat large, does not appear to be abnormal. The sella turcica is wide and shallow, measuring 10 mm. in length, 22 mm. in width and 5 mm. in depth. The pituitary must have bulged at the sides, when *in situ* to occupy such cramped quarters and probably expanded antero-posteriorly after it was removed. The sella turcica is somewhat discolored and reddened. Nothing abnormal is noted in the case of the mammillary bodies or tuber cinerium.

Microscopic Examination

Microscopic Diagnoses: Endothelioma of the dura with metastasis or double incidence, involving tentorium and stalk of the hypophysis. Slight adenomatous hyperplasia and marked focal sclerosis of the hypophysis. Sclerosis and colloid struma of thyroid. Rather extensive and active thymic rests. Adrenal hyperplasia and bilateral adenoma. Autodigestion of pancreas and mild acute pancreatitis with fatty invasion of the organ and fibrosis. Fibrosis of ovary with subacute oöphoritis.

Myocardial hypertrophy, focal fibrous myocarditis, coronary sclerosis. Chronic passive congestion of lung, liver and spleen. Pulmonary anthracosis and healed tuberculosis with hypostatic congestion. Perisplenitis and fibrous perihepatitis. Chronic cholangitis. Chronic vascular and intracapillary glomerulonephritis. Uterine adenoma (polyp) and chronic hyperplastic endometritis in a senile, fibrotic uterus. Senile atrophy of the brain.

Microscopic Appearance of the Tumors and Endocrine Glands

Tentorial Tumor. This is composed of slender, apparently fusiform cells with a rich cytoplasm which shows no demonstrable fibrillae with Van Gieson's, Bielschowsky's or Mallory's phosphotungstic acid hematoxylin stains. Mitotic figures are present in moderate numbers, usually occurring in small cells that lie between the tumor cells. The arrangement of the growth is in sheets and concentric whorls, as shown in Fig. 2. The sheet-like leashes of cells that one sees running through the tumor have larger nuclei than those in the whorls. Tumor giant cells may be found occasionally. Between many of the cell masses one finds deposits of dense collagenous tissue which stain selectively with appropriate dyes. Occasionally a corpus amylaceum is encountered and calcification of the collagen masses is sometimes observed, as well as hyaline degeneration thereof. The tumor has infiltrated the dura to a moderate extent.

Infundibular Tumor. This was discovered only after microscopic examination was made. It lies close to the stalk of the hypophysis in the dural sheath and is almost identical in its appearance with the tentorial growth, but tends to grow in wider sheets (Fig. 3). It infiltrates the dura and has almost penetrated it in places (Fig. 4). Small islands of tumor cells are seen in the dural spaces at some distance from the main growth, indicating metastasis. The masses of collagen and the psammomatous bodies are not as numerous in this tumor as in that on the tentorium, but mitotic figures are rather more abundant.

Hypophysis. The gland shows a definite hyperplasia, amounting almost to a struma and there is much sclerosis near the site of the tumor in the anterior lobe (Fig. 5). The appearance of the gland does not differ very much from that noted in pregnancy, but this woman was neither pregnant nor had she borne children. All the cells of the anterior lobe contain neutral fat in coarse drops and masses in the chromophil and in very fine dust-like granules in the chromophobe cells. This substance stains yellow to orange with Sudan III, rose-pink with Nile blue sulphate and from brownish yellow to black with osmic acid. Fig. 6 was photographed from a frozen section stained with Sudan III. There is so much black and brownish material in the Bensley stain, that little of the cytoplasmic

details can be made out. There is definite sclerosis only in that portion of the gland that abuts on the tumor. The pars intermedia contains the usual colloid masses in its acini; but some of them have increased until they constitute retention cysts. The pars posterior does not seem very abnormal, as compared with a normal control.

Thyroid. As seen in Fig. 7, this is rather less rich in colloid than it should be, as that substance is thinned out, vacuolated and scalloped at the periphery, although the acini are larger than normal. The connective tissue is increased in amount. No embryonal acini are found.

Parathyroid. This is very much congested and contains some retention cysts filled with colloid material, but it is not abnormal for a woman of advanced age.

Thymus. Although it consists chiefly of fatty tissue, there are numerous small islands of thymic tissue which assume respectable proportions under the microscope and show Hassal's corpuscles and "thymic reticulum cells," as well as rather sparsely distributed lymphocytes. There is no necrosis of the Hassal's bodies which are apparently as well preserved as they would be in a child of a few years of age.

Suprarenal Glands. Both of these are hyperplastic and the central softening, noted at necropsy, is represented by poor staining and dissolution of the tissue of the medulla. The tumors contained in these glands are composed of cortical cells very lawlessly arranged (Fig. 8); they may be grouped into glandular complexes, or dissociated. There is no suggestion of hypernephroma. Areas of hemorrhage and groups of pigmented phagocytes are seen and lymphocytes have infiltrated the gland rather abundantly in places.

Pancreas. Unfortunately this has undergone rather extensive postmortem autodigestion and shows much necrotic parenchyma. As there are areas of polymorphonuclear infiltration, one wonders whether it was a terminal infiltration due to this process, or whether there was an early inflammatory reaction in some way connected with the cholecystitis and cholangitis. Where the pancreatic tissue has escaped this process, the islets and the parenchyma are apparently normal. There has been considerable invasion of the organ by adipose tissue and fibrous connective tissue and the fat cells have been affected by the pancreatic lipase and appear as they do in "fat necrosis."

Ovary. There is marked senile sclerosis, many corpora hyalina, a number of follicular cysts and, at one pole, a collection of endothelial phagocytes and some epithelial rests resembling kidney tubules.

Other Organs. Microscopic examination of the other organs does not show anything that adds greatly to the value of this paper and the diagnoses have been listed elsewhere. The skeletal fat is not abnormal, nor do the nerves it contains show any striking changes in appearance. The brain fails to show any hemorrhages and the only demonstrable lesions are porosity and gliosis, such as one would expect to find in senile atrophy. There is a generalized lymphocytic infiltration of a very insignificant degree and the small glia cells are notably increased in number.

Discussion

We could discuss this case with a great deal more assurance had we been able to study it longer while the patient was alive. The meagerness of the history and the impossibility of observing her over an extended period of time make it difficult to correlate the symptoms that may have been present with our pathologic findings. Our patient showed the following signs and symptoms of adiposis dolorosa: huge fat masses on the body and extremities, but no adiposity of the head, forearms, hands, legs or feet; a history of recent epileptiform convulsions and at least a transient psychosis (uremia should be considered here); subnormal temperature; asthenia; ulcers on both shins (possibly varicose); but no history of pain or tenderness over the fat masses or nerve trunks. Had she lived longer and retained consciousness, she might have been able to enlighten us on this point and she may have had such symptoms in the past without her friends hearing of them.

The necropsy findings coincide very accurately with those in undoubted cases of adiposis dolorosa. The very definite lesions in practically all the endocrine glands are striking: pituitary sclerosis and hyperplasia, with a tumor; sclerosis and changes in the colloid content of the thyroid; persistent and well preserved thymic rests; adenoma of both suprarenals, with hyperplasia; ovarian sclerosis and atrophy; and definite, though slight, changes in the pancreas. Besides these, we see changes in the cranial bones, with exostoses and definite cerebral atrophy, with some generalized thickening of the dura.

How is one to interpret these lesions? We may rule out the ovarian sclerosis on the obvious basis of senility, but we do not know how long it was present. We may ignore the pancreatic changes as the result of postmortem autolysis and senility; we may disregard the thickening of the dura, skull and meninges and the cerebral atrophy, as representing racial and senile changes. We cannot, however, dismiss the pluriglandular pathologic condition of the endocrine system in general.

Perhaps the most striking thing about the case is the presence of two atypical dural endotheliomas, one involving the stalk of the hypophysis. While this tumor is usually essentially benign and produces much reticulum, our tumors were evidently malignant (as judged by the primitive type cell, the presence of mitotic figures, the infiltration and the possible metastasis) and they produced no reticular or collagenous matrix. We cannot say that the tiny tumor of the hypophyseal stalk was metastatic from the tentorial tumor, but that is the natural inference. If that were true, how could one explain the long-standing adiposity and asthenia of the patient? Possibly by supposing that the over-acting hypophysis long antedated and, later, predisposed toward tumor growth by stimulating it as it did the endocrine organs elsewhere. Be that as it may, the hypophysis seems to present more marked changes than do the other endocrine organs in this case.

Dercum [1] was inclined to ascribe his syndrome to a lesion of the thyroid. Cushing [3] believes that many cases reported as adiposis dolorosa "are actually examples of disturbed metabolism secondary to diseases of the ductless glands." He does not consider this disorder to be a clinical entity, maintaining that it begins as a disturbance of the pituitary body affecting the thyroid secondarily. In later papers Dercum seems to be of the same opinion. Cushing reports an interesting case with all the typical features of Dercum's disease, in which a necropsy revealed no change in the pituitary, but generalized and extreme cerebral atrophy; he proposes that such cases be termed "adiposis dolorosa cerebralis." Price [4] found changes in the pituitary gland in both of his cases, but believes that those in the thyroid are of equal importance. What of the suprarenals? They, too, have shown strikingly constant pathologic changes in this disease.

The protocols of the sixteen cases in the literature and of ours,

point out quite clearly that the findings are not compatible with the assumption that adiposis dolorosa is a clinical entity and that Cushing is correct. The hypophysis has shown nothing at all, slight lymphocytic infiltration, adenomatous hyperplasia and sclerosis or it has been the site of tumors. The thyroid picture varies from nothing pathologic to sclerosis or even colloid struma. The thymus has not been mentioned hitherto, so that our case is apparently unique in this respect. The suprarenals have shown adenomatous hyperplasia pretty constantly. The gonads have been sclerotic, or "defective," which is compatible with the advanced age of most of the patients described and may not be very important unless constantly found in younger subjects. The fact remains, however, that something is usually wrong in most, if not in all of the endocrine glands in these cases and we must find out why this is so before we can declare the matter settled. Is not adiposis dolorosa merely the typical picture of a majority of a certain group of cases in which the endocrine system is involved and the fat metabolism interfered with?

Conclusions

The pituitary body is apparently at fault in this case, as in most of those that have come to necropsy. The changes in the other endocrine glands seem to follow as a result of this. It seems reasonable to suppose that sclerosis of the thyroid, persistence of thymic tissue in a patient of 60 years and adenomas of the suprarenals could be explained on a basis of overstimulation by the hypophysis. One hesitates at speculating too broadly on this subject for fear of allowing one's conclusions to become purely metaphysical and unwarranted by the facts at hand. It is justifiable, however, to ascribe the pathologic findings in this case to a profound disturbance in the endocrine system, probably arising as a result of one of the lesions found in the hypophysis cerebri.

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DESCRIPTION OF PLATES

PLATES 47–50

FIG. 1. Photograph of the patient after necropsy. Note the comparatively normal size of the legs and forearms, the moderate adiposity of the head and the great masses of fat on the trunk, arms and thighs. The ulcers on the ankles are also visible.

FIG. 2. Section of the tentorial tumor. A mass of hyaline colloid is at the center. Hematoxylin and eosin stain. x 300.

FIG. 3. Section of tumor on hypophyseal stalk. A corpus amylaceum is clearly shown. Note whorls. Phosphotungstic acid hematoxylin stain. x 300.

FIG. 4. Tumor infiltrating the dura over the hypophyseal stalk. Hematoxylin and eosin stain. x 300.

FIG. 5. Section from a distinctly sclerotic portion of the hypophysis. Hematoxylin and eosin stain. x 300.

FIG. 6. Frozen section of hypophysis stained with Sudan III, to show fat droplets (black in the photomicrograph). x 300.

FIG. 7. Section of thyroid, showing vacuolization and erosion of colloid and marked sclerosis of supporting framework of gland. Hematoxylin and eosin stain. x 300.

FIG. 8. Section through an adenoma of the suprarenal, showing the composition of the tumors in this case. Hematoxylin and eosin stain. x 300.

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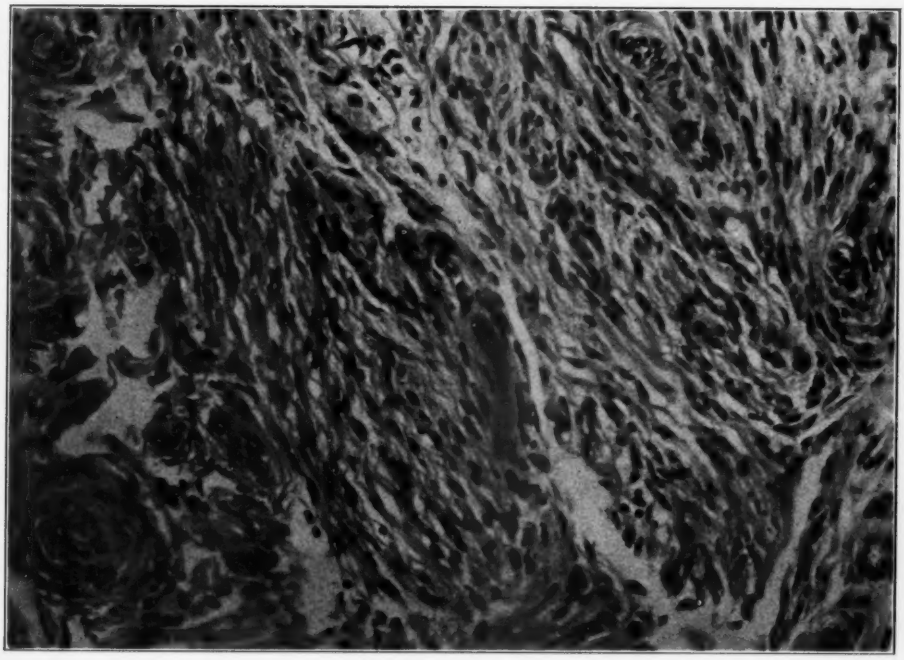

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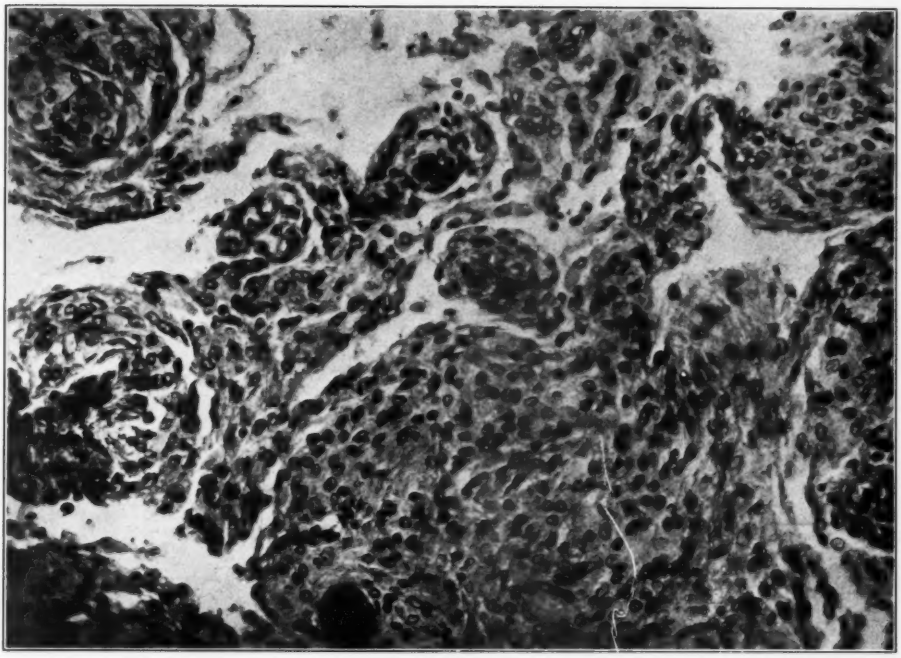
Foot, Good and Mènard Adiposis Dolorosa



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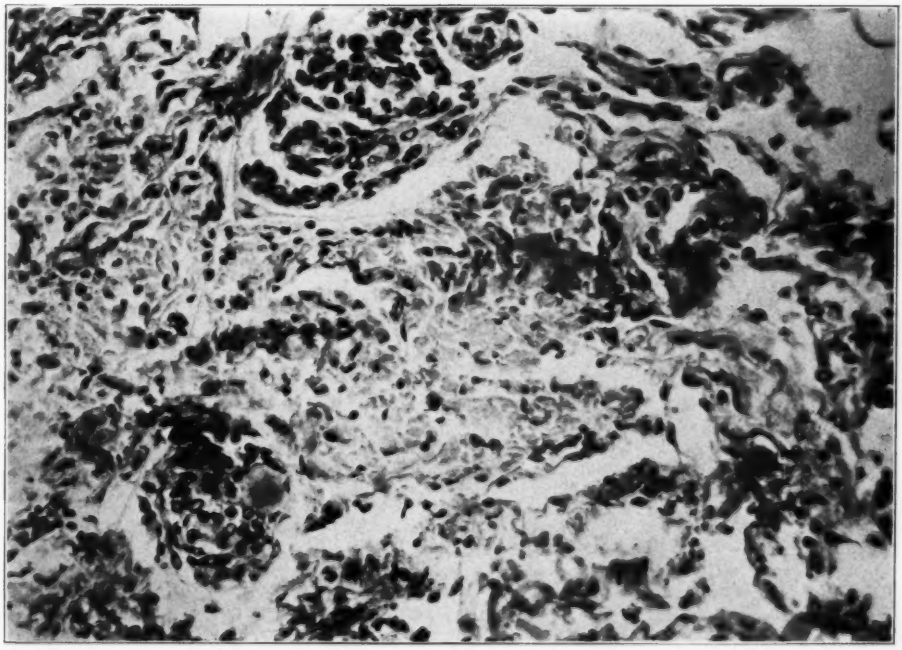

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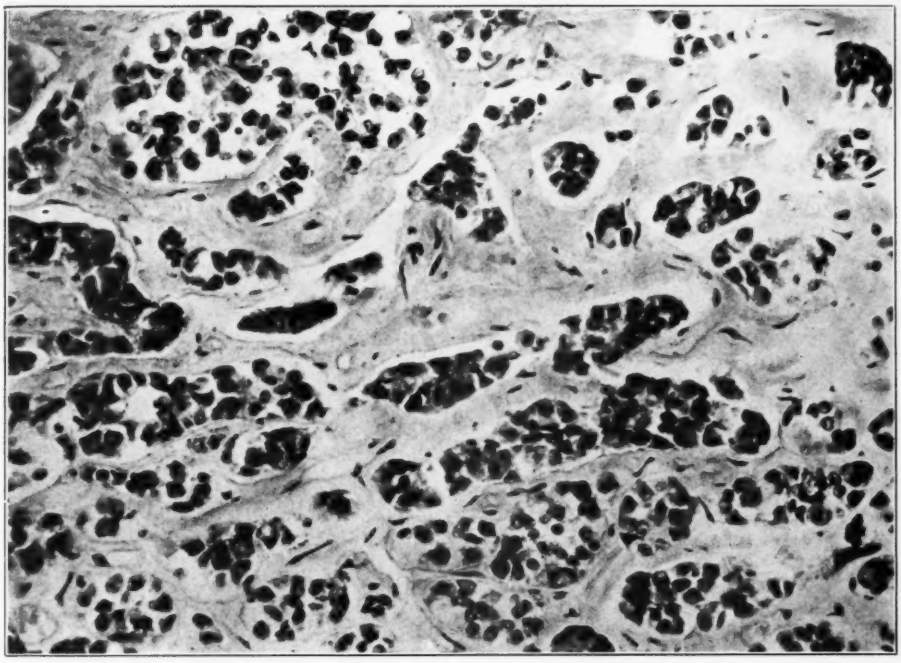

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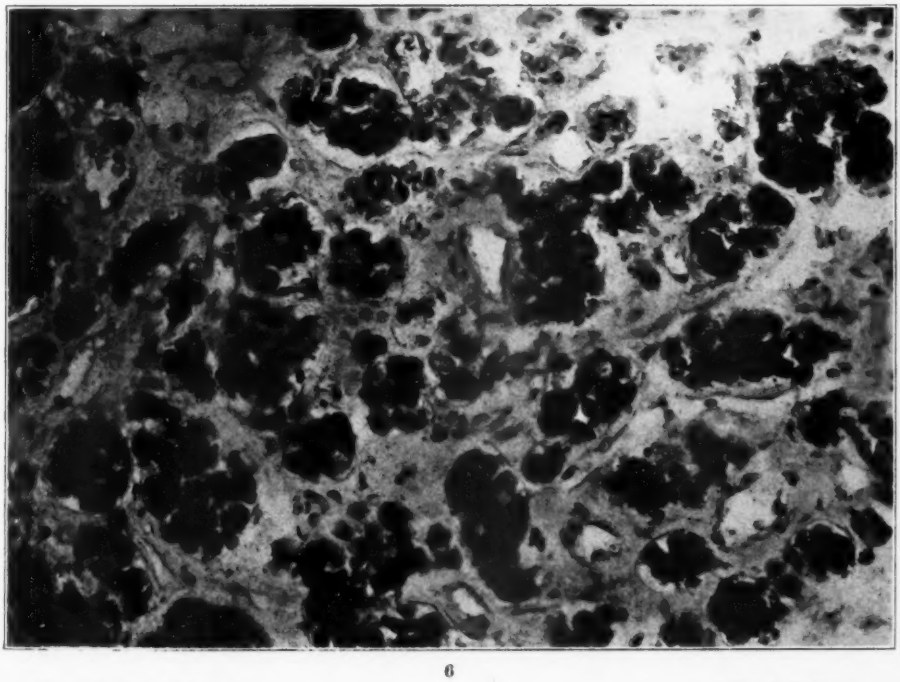

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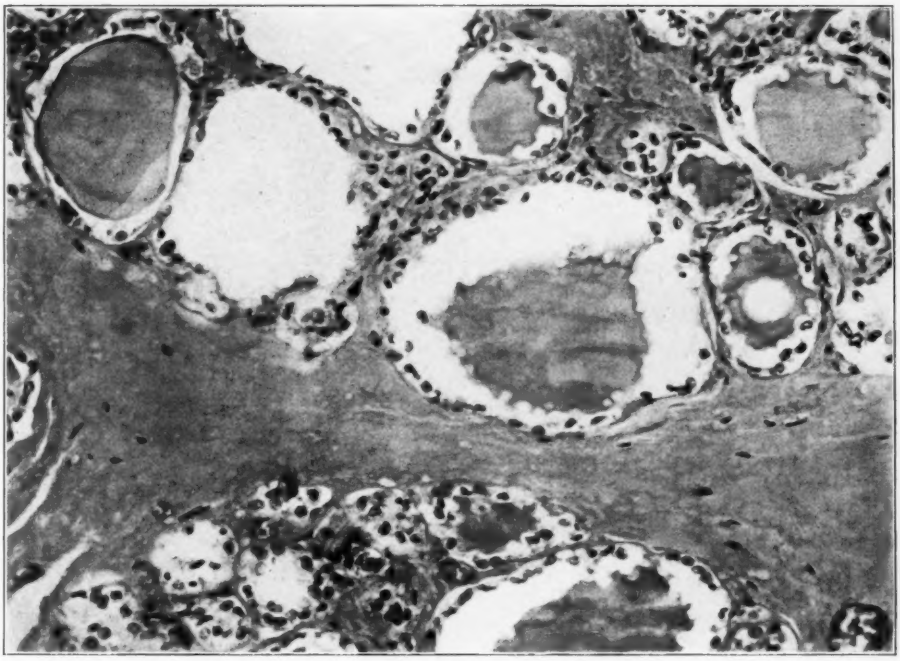

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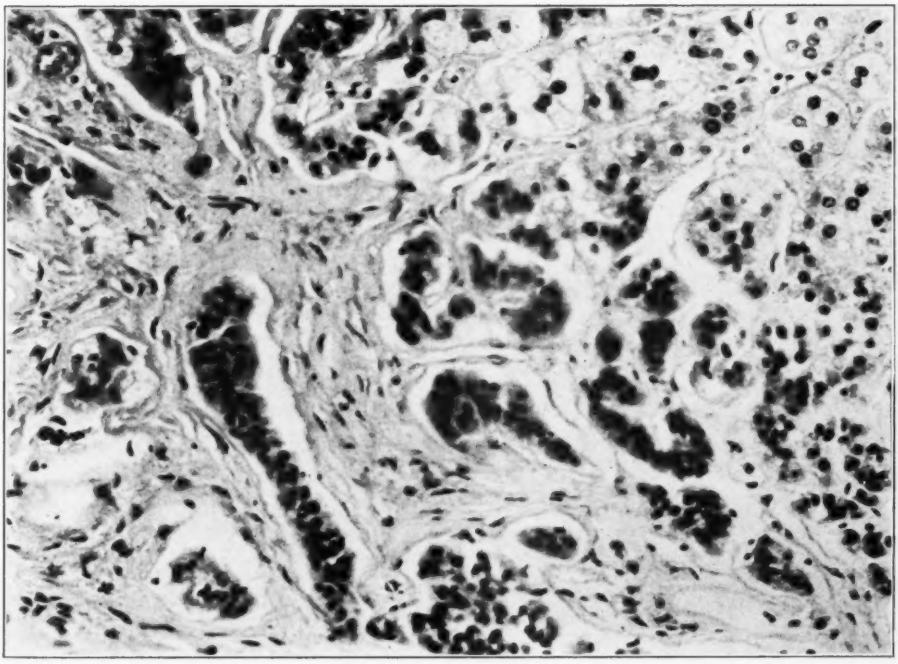

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Foot, Good and Mènard Adiposis Dolorosa

THE HISTOPATHOLOGY OF THE SUBCUTANEOUS LESIONS IN TULAREMIA IN MAN *

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INTRODUCTION

The question of tularemia was brought acutely to our notice in December 1925, when Maclachlan, Fetter and Cratty [1] reported the first two cases from Pennsylvania. Since then, a third case has appeared in the Mercy Hospital on the surgical service of Dr. Weil, and within a few weeks three others in different hospitals in Pittsburgh.

Our interest in the disease was stimulated by the study of the tissue reactions in subcutaneous lesions obtained from Dr. Weil's patient by biopsy. These tissues form the basis of the present paper. No attempt will be made to cover the history of tularemia which Francis [2] has already done, nor to review its growing literature except that part pertaining to the pathology of the disease.

CASE REPORT

Mrs. M. H., aged 48, was admitted to the hospital on Jan. 30, 1926, complaining of pain and swelling in the right arm and axilla. The relevant points in her history are those related to the chief complaint. She was employed in a butcher's shop and on Nov. 19, 1925, while at work dressing rabbits for sale, she scratched her right thumb on a splintered rabbit bone. The animals were of the common wild variety and had been shipped from Kentucky. The wound was slight and was given no attention. Three days later the thumb became painful, and the patient had two severe chills with nausea. When seen by a physician the next morning, she had a fever of 105 F and there were "red streaks" observed on the forearm as far as the elbow.

After remaining in bed with wet dressings for a few days, the thumb was incised and pus was found. Two weeks later the primary

* Received for publication April 10, 1926.

lesion again required incision, and at about this time inflammatory nodules appeared on the flexor surface of the forearm, following the distribution of the lymphatics. These appeared after chills, fever and subjective symptoms such as had accompanied the infection in the thumb. Some of these lesions required drainage. The entire illness was characterized by weakness and malaise. As there was no real improvement she was sent to the hospital, coming in about ten weeks after injury.

At the time of admission, she appeared to be in fair general condition, the peculiar lesions of the right arm being the only important finding. The thumb showed a recently healed wound. At the wrist and elbow and in the axilla were small sinuses discharging a seropurulent fluid from chronic indolent inflammatory foci. An indurated subcutaneous nodule about 1.0 cm. in diameter was noted near the midpoint of the forearm, where the overlying skin was dull purplish red. A fluctuating mass could be felt in the axilla, but here the skin showed no change as this mass was more deeply placed. The entire group of nodules followed the lymphatic distribution on the flexor surface. Later (about March 9), the lymphatic involvement became unmistakable. The superficial lymphatics could be palpated through the skin of the forearm as a beaded cord-like structure.

Further investigation at that time revealed little of a positive nature. Her temperature was 97.6 F. A blood count showed 12,000 leucocytes with 63 per cent polymorphonuclear neutrophiles. The blood pressure was unusually low, 86 systolic and 60 diastolic, corresponding with the depressed state. X-ray examination of the thumb showed no bone involvement. The blood Wassermann was negative.

On Feb. 1, 1926, the nodule on the forearm and the axillary swelling were drained. Both contained a creamy light greenish yellow pus which showed no organisms by the usual stains, but contained many pus cells. Cultures on ordinary media showed no growth from the nodule on the forearm, though a *Staphylococcus albus* was recovered from the axillary lesion. A biopsy was done on the nodule on the forearm at the time of incising it (first biopsy).

No special reaction followed this operation. The patient was not bedfast, but it was thought better to confine her to bed owing to her peculiar weakness and malaise. On Feb. 7, 1926, a temperature of 99.8 F was recorded with chill, nausea and increased subjective symptoms. The upper arm became tender and painful over the

biceps region and in a few days two definite subcutaneous nodules appeared. A blood count at this time showed a slight decrease in the total leucocytes and in the polymorphonuclear neutrophiles as compared to the previous count. On Feb. 11, 1926, she developed another rather severe chill and slight rise in temperature. This reaction was likewise accompanied by increased malaise and nausea. It was the sixth or seventh exacerbation and as before a new lesion soon developed, this time in the axilla near the two earlier ones. On Feb. 24, 1926, the two subcutaneous nodules on the upper arm were excised intact with the skin and subcutaneous tissue (second biopsy). Both biopsy sites healed readily; the second by primary union, while the first cleared up more readily than the axillary lesion from which no tissue was excised. However, the secondary infection in the axillary focus explained the delay in healing.

On February 27, the patient complained of pain and tenderness in the right lumbar region. Examination revealed a definite tender mass here and a similar but less tender one on the left side. These have slowly regressed since that time. (One of Hodges'[3] patients developed nodules in the thoracic region of the back.) These lesions appeared after a chill which was accompanied by flashes of heat over the body, particularly felt in the right arm and in the legs. Sattler's[4] case had the same subjective symptoms.

Tularemia was considered as a diagnosis from the history and clinical findings. In view of the negative bacteriologic results and especially after obtaining an unusual microscopic picture in the first biopsy, a sample of the patient's serum was sent to Dr. Edward Francis, Hygienic Laboratory, Washington, D. C. On Feb. 10, 1926, he reported the agglutination of *Bacterium tularense* by this serum in dilutions of 1:10, 1:20, 1:40, 1:80 and 1:160, but not higher; which, he stated, confirmed our diagnosis. On Feb. 19, 1926, he reported the same titer on a second sample taken ten days after the first. A third sample, taken March 20, 1926, again showed the same titer.

Further studies leading to a determination of the causative agent were carried out on the tissue, but like the bacteriologic analyses were chiefly valuable as negative evidence. Sections stained by the Gram-Weigert and Ziehl-Neelson methods revealed no bacteria of any type. Twort's[5] light green-neutral red mixture was then tried in an attempt to stain *Bacterium tularense* in the tissue. This also

gave negative results. Animal inoculation was not done. The patient is slowly convalescing, and no further operative interference has been indicated.

Pathologic Report

The first specimen obtained consisted of a wedge-shaped piece of tissue from the indolent-looking purplish red inflammatory nodule on the flexor surface of the right forearm. When the nodule was incised a few drops of creamy, greenish yellow pus flowed out. The biopsy material was then taken and dropped immediately into Zenker's fluid. It represented a quadrant of the complete lesion with the overlying skin.

The second specimen was removed from the same aspect of the upper arm. It represented a more recently developed lesion and consisted of two small subcutaneous nodules lying close together and easily felt through the skin. These were excised widely, together with the overlying skin. The material was fixed in Zenker's fluid and sliced after it had hardened slightly. The nodules were small abscess-like structures measuring respectively 0.6 and 0.3 cm. in diameter, located in the subcutaneous tissue. They showed dull yellow walls and contained a drop or two of creamy light greenish yellow pus. There was no gross evidence of hemorrhage or of congestion.

The second biopsy furnished better material, since the lesion thus obtained was complete and in an earlier stage of development. It will therefore form the basis for the microscopic description, and additional features illustrated by the more advanced lesion will be described in the appropriate place.

Histopathologic Report

The sections show circumscribed inflammatory nodules lying below the dermis and in the fatty areolar tissue, rather than in a lymph node. Spaces representing adipose tissue cells are noted throughout the nodules. The process apparently originated in lymphatics. The inflammatory reaction is somewhat unusual.

A typical inflammatory nodule shows a necrotic center, in which granular débris is packed with polymorphonuclear leucocytes and degenerating mononuclear cells of the endothelial type. Sometimes a degenerating giant cell lies free in the necrotic material. Surround-

ing this and dividing it from the living tissue is a narrow zone (not more than five or six cells deep), of granular, partly degenerated endothelial leucocytes which lie in a delicate, irregular meshwork of fibrin. Just beyond this is found a clearly marked zone of newly formed tissue having all the essentials of granulation tissue, though with certain differences affecting both the fibroblast and the capillary elements.

The capillaries in this zone of newly formed tissue are few and small, with narrow lumina as a result of hyperplasia of the endothelium. The reactions in capillaries and small vessels are important and will be referred to again. The fibroblasts are numerous, large and closely packed. They are plump enough to resemble flattened endothelial cells, and their radial arrangement suggests that commonly seen in caseous tuberculous lesions. Phosphotungstic acid hematoxylin and Mallory's anilin blue stains demonstrate fibroglia fibrils in these cells as well as areas of early collagen formation in parts of the fibroblastic zone, thus identifying the predominating cells of this zone as fibroblasts.

Inflammatory cells of all types, including many endothelial phagocytes, are scattered throughout this zone in about equal numbers without forming definite collections. Further, a striking and unusual finding is encountered in the presence of many large giant cells much like the Langhans type. These are practically confined to the fibroblastic zone.

The outermost zone of the nodule is made up of a dense chronic inflammatory cell exudate in which lymphocytes and plasma cells predominate. In the areolar tissue beyond this, the same cell types form dense, perivascular collections. Occasionally a small vessel shows definite perivascular and medial inflammation. Some adipose tissue cells are partly surrounded by endothelial cells, with early giant cell formation. Capillaries are somewhat more numerous in this zone than in the inner fibroblastic one; but in both locations, they show the remarkable proliferative reaction of the endothelial linings briefly referred to above. The usual wide, thin-walled capillaries of granulation tissue are not conspicuous. Instead, most of the capillaries are rather narrow. Endothelial hyperplasia is most marked in the sections from the larger, more advanced lesions of the first biopsy. In any section many examples of the reaction can be found, usually with one or two showing complete obliteration of the

lumen. In some, mitotic figures appear in the endothelial cells, indicating marked proliferative activity. The capillaries all contain many polymorphonuclear leucocytes in and about them. Those with piled up endothelial linings show polymorphonuclear leucocytes lying between the cells of the thickened wall.

Finally, and further contributing to the granulomatous character of the lesion, there is noted the development of small secondary necrotic foci in the wall about the large necrotic center. These are sometimes merely collections of endothelial cells with a small giant cell. Again they are more advanced, showing necrotic centers filled with polymorphonuclear leucocytes. These centers are surrounded by a few endothelial cells beyond which lies a fibroblastic zone. In a word, the secondary foci are small replicas of the large lesion. These can often be found related to obliterated capillaries. The heavier fibrous bands of the reticular tissue appear to have a slight limiting effect on the extension of the lesion. At the same time they show fibroblastic proliferation as an evidence of an inflammatory reaction in which they partook to some degree.

Through the kindness of Dr. A. J. Bruecken of the St. Francis Hospital and Dr. J. W. McMeans of the St. Margaret Memorial Hospital, we have been permitted to study material from two of the three other Pittsburgh cases. In each the diagnosis was verified by agglutination tests, the titers running up to 1:320 and 1:640 respectively (Francis). Both specimens consisted of axillary lymph nodes. The histopathologic findings are identical in all essentials with those found by us in the subcutaneous nodules.

Discussion

We have been interested in presenting a description of the subcutaneous lesions in human tularemia, since no detailed study of them is available in the literature. Sattler,[4] in 1915, reported the excision of a small nodule from the conjunctival sac which Woolley described as "a granuloma without giant cells apparently occurring in a lymph gland." Ohara, quoted by Francis and Moore,[6] reported the pathology in an axillary lymph gland as follows: "Histologic examination of the lymph gland excised in the human experimental case showed round cell infiltration, dilatation of the blood vessels, extravasation of blood, small pus cavities, caseation and giant cells." The only

other description of human lesions of any type is that of Verbrycke [7] who reported a fatal case with necropsy. Francis [8] also examined this material and wrote of it in part as follows: "Microscopic sections of spleen and liver showed the small areas of focal necrosis typical of the disease in guinea-pigs and rabbits . . . the enlarged peribronchial lymph glands and nodules found in the lung substance showed the areas of focal necrosis; there were giant cells in the peribronchial lymph nodes. No tubercle bacilli could be demonstrated in lung, spleen or liver." The lymph nodes from the other recent cases in Pittsburgh, which we have cited briefly above, complete the list of human lesions which have come to microscopic examination.

The clinical picture of our case corresponded well with the cases of this type in the literature. It particularly resembled that of Hodges.[3] The gross appearance of our specimens was also typical of the human lesions of Hodges,[3] Verbrycke,[7] Shelton,[9] Sattler [4] and others, as well as of the two more recent Pittsburgh cases.

The general resemblance to the described animal lesion was evident. Woolley,[10] in 1915, published the first microscopic study of tularemic lesions, made on the experimental animals of Wherry and Lamb [11] (1914). He described the reaction as a primary necrosis, with suppuration only in the skin lesions. He found no evidence of any marked proliferation of endothelial cells. The earliest change he believed to be degeneration of a focal area, with beginning karyorrhexis. At this stage he found a few lymphocytes, and noted that the polymorphonuclear leucocytes appeared after degeneration of tissue had occurred, adding that were there more endothelial proliferation, the lesions might resemble those seen in the liver in typhoid fever. Councilman and Strong [12] (1921), described clearly the pathologic histology in the acutely fatal lesions of animals. Their report is of the greatest interest in this connection, since they described the same basic reactions in the animal tissues that we found in the human. They stressed endothelial hyperplasia and the mononuclear character of the early cellular exudate, noting that the polymorphonuclear leucocytic response was entirely secondary. They were able to stain the *Bacterium tularense* in the liver cells, and also in the vascular endothelium. In summing up, they stated that "The essential lesion is infection of the endothelial cells, general but more marked in the vessels of certain organs." Ledingham and Fraser [13] (1924) published the only other microscopic study of

experimental lesions. They emphasized the demonstration of *Bacterium tularense* in the tissues; otherwise their descriptions coincided with Woolley's.[10] They failed to note the vascular changes and endothelial cell exudate described by Councilman and Strong.[12]

We feel it is evident that the descriptions available in the literature (with the exception of that of Councilman and Strong [12]), are not entirely clear and that they offer no basis for an explanation of the peculiar necrotic lesions of tularemia. It is also quite evident that the inflammatory reaction we have described is a granuloma. This character does not seem to appear in animal lesions which are far more acute than those of man. The chronic clinical course typical of the disease in man is suggestive of a granulomatous type of reaction.

In view of this granulomatous character, the explanation of the human lesions we have studied becomes fairly simple. They are in some respects similar to the reactions in typhoid, syphilis, actinomycosis and blastomycosis, though at first glance the suggestion of a caseous tuberculous lesion is very strong. The infection is evidently blood-borne in animals, while in the usual human case its manifestations suggest a local lymphatic spread, accompanied by a marked toxemia. The possibility of a temporary and even recurrent bacteriemia in the human must also be considered. The type of injury is apparently mild, though more active than that of tuberculosis. The reaction tends toward healing, and this process is greatly facilitated by drainage.

To confine the discussion to the subcutaneous lesion, the first reaction is one leading to endothelial proliferation in capillaries with the local production of wandering cells, resulting in endothelial collections and giant cell formation about the bacteria. Excessive capillary reaction of this type tends to narrowing and even obliteration of the capillaries. Mitoses indicate that this process is quite active. As a result of these intracapillary changes, necrosis takes place in the areas rendered anemic. The action of bacterial toxins must also be considered, but a capillary obstruction best explains the sudden and relatively extensive necrosis in which degenerating endothelial and giant cells can still be made out.

The presence of necrosis stimulates a marked polymorphonuclear leucocytic exudate which infiltrates the necrotic area and plays a part in bringing about softening. The fixed tissue response about the

necrosis consists of a cellular granulation tissue, in which are many giant cells. The endothelial proliferation continues and, with further obliteration of capillaries, small secondary necrotic foci are formed in the granulation tissue wall about the primary area of necrosis. The numerous giant cells in the fibroblastic zone indicate the sites of beginning secondary necrotic foci.

In the meantime, polymorphonuclear leucocytes continue to migrate to the necrotic area. They may be seen filling the capillaries, emerging from them and lying in their vicinity. Even from the vessels with piled-up linings, the polymorphonuclear leucocytes still continue to wander out into the tissues. We find sometimes that a completely obliterated capillary, a mere whorl of endothelial cells, shows many polymorphonuclear leucocytes in the interstices between the endothelial cells obstructing the lumen.

These changes are interesting as tending to show that local capillary endothelium may undergo great activity in the production of wandering endothelial cells, as has been claimed by Mallory,[14] Mallory and Medlar,[15] Foot,[16] Permar[17] and others. The presence of mitotic figures in the cells of the capillary walls is also in favor of this theory. It must be admitted that many of the wandering endothelial cells may have originated in the more commonly active endothelial beds; but the capillaries do not contain free mononuclear phagocytes in even appreciable numbers, though this cell forms a good part of the local exudate.

The perivascular lymphoid and plasma cell infiltration found at the periphery of the lesion is characteristic of any chronic inflammatory process, and notably of the granulomas. The involvement of the walls of small vessels is apparently by extension from the perivascular lymphatics. The reaction about fat tissue cells is the result of injury incident to their inclusion in the involved area.

Conclusions

1. The histopathology of the subcutaneous lesion in human tularemia is described in detail.

2. The lesion presents the microscopic characteristics of a granuloma.

3. The tissue reaction may be summarized as follows: (*a*) primary massing of endothelial cells with giant cell formation; (*b*) endothelial

hyperplasia with obliteration of capillaries; (*c*) necrosis with polymorphonuclear leucocytic infiltration and liquefaction; (*d*) development of small secondary lesions which pass through the same stages and tend to fuse with the primary one; and (*e*) delayed healing by organization.

The authors wish to express their appreciation to Dr. S. R. Haythorn for his kindness in preparing the photomicrographs used in this paper.

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DESCRIPTION OF PLATES

PLATES 51–54

FIG. 1. Low-power field, showing the general structure of the lesion and the surrounding reaction.

FIG. 2. One angle of the lesion, showing the necrotic center filled with polynuclears and surrounded by a zone of granulation tissue containing giant cells. Capillaries are few and small.

FIG. 3. High-power field of the margin of the necrotic area, showing the margin of large mononuclear cells.

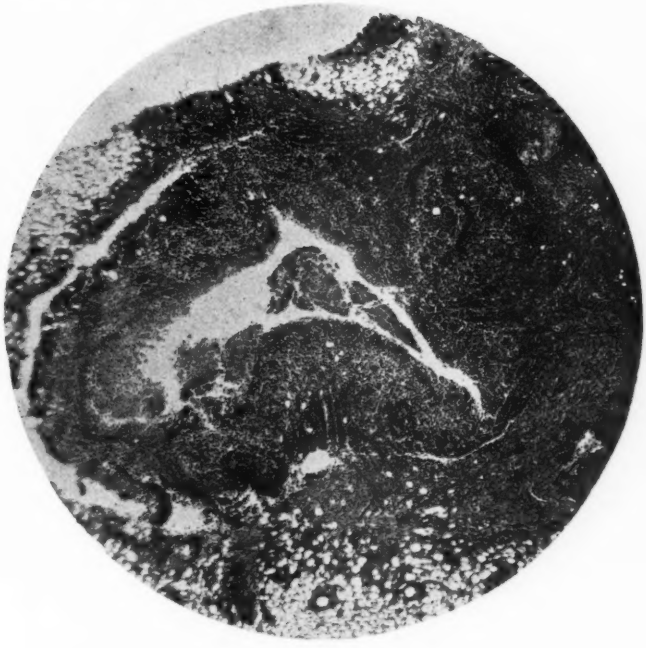
FIG. 4. Early secondary lesion in the fibroblastic wall, showing collections of mononuclear cells and giant cells.

FIG. 5. More advanced secondary lesion, showing beginning necrosis and a large giant cell at the margin.

FIG. 6. Extreme examples of proliferation of capillary endothelium in the wall of the lesion.

FIG. 7. Two mitoses in a capillary.

FIG. 8. Mononuclear collections and giant cell formation about injured adipose tissue cells in the areolar tissue involved in the reaction.



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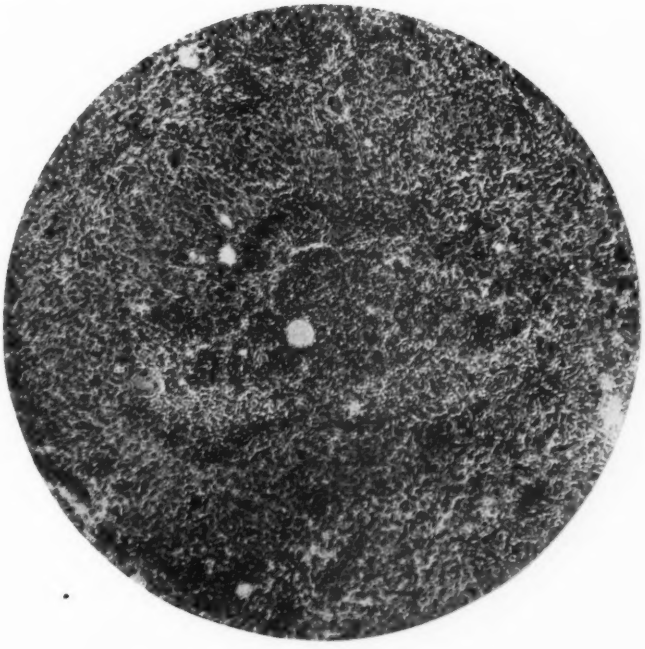

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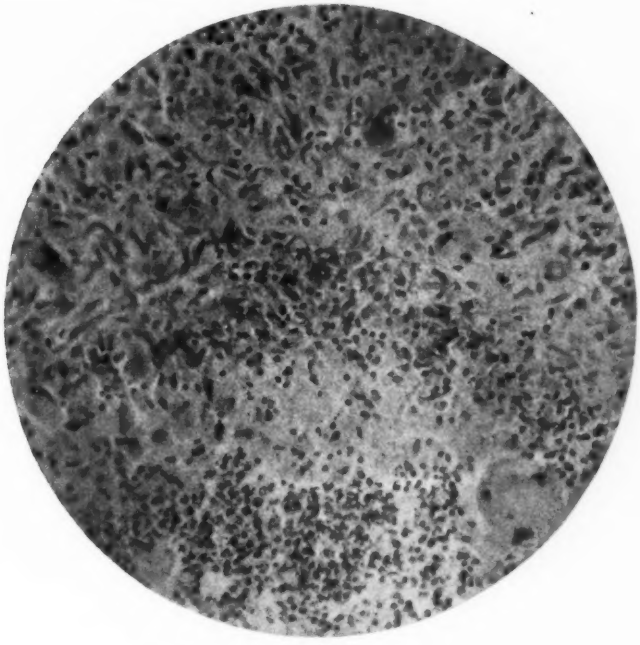
Permar and Weil Subcutaneous Lesions in Tularemia in Man



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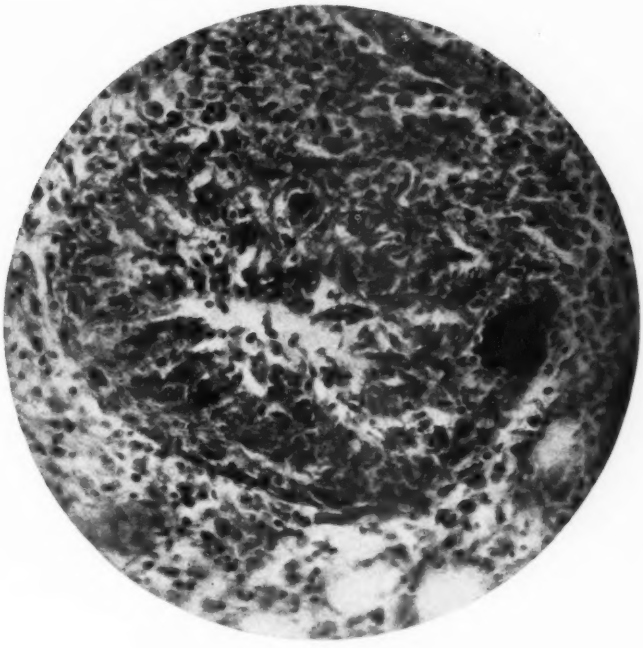
Permar and Weil Subcutaneous Lesions in Tularemia in Man



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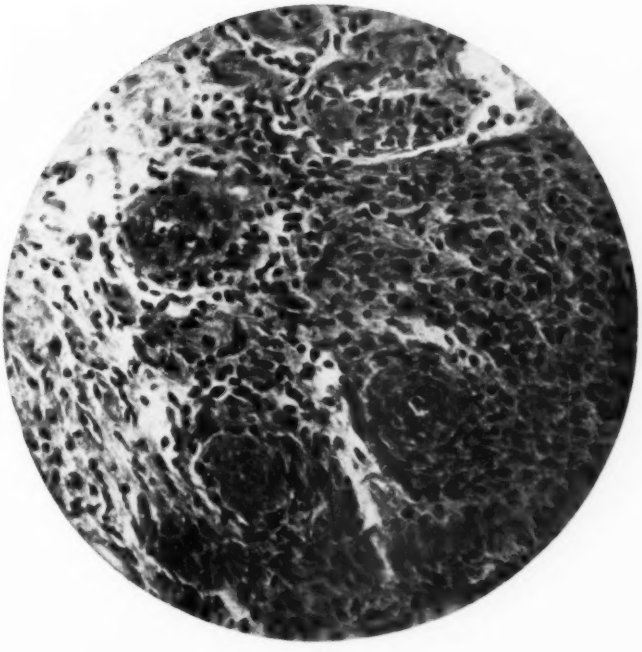

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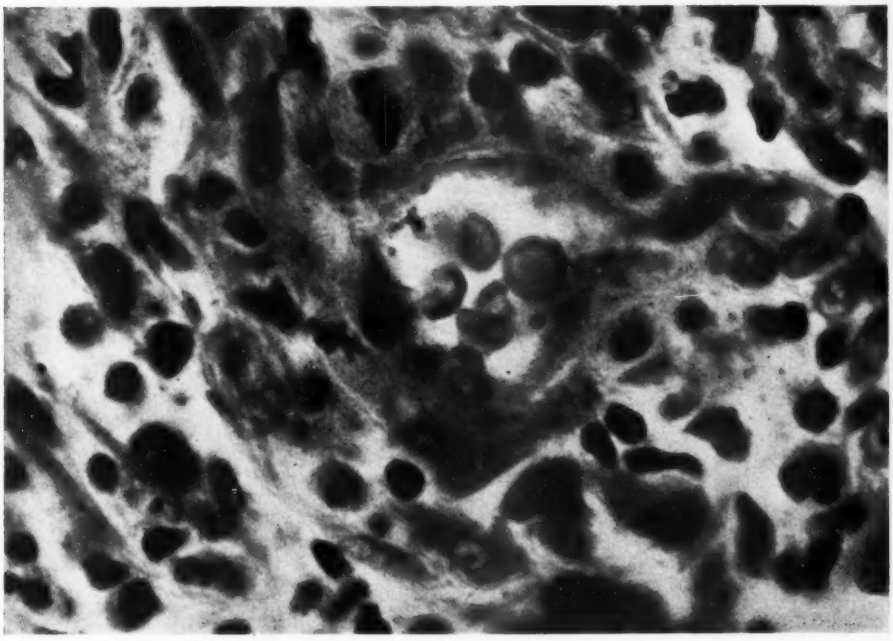

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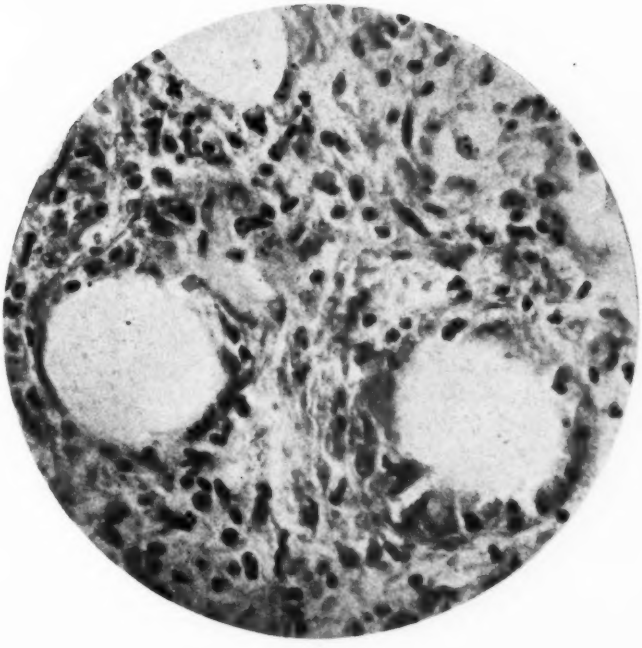

8

Permar and Weil Subcutaneous Lesions in Tularemia in Man